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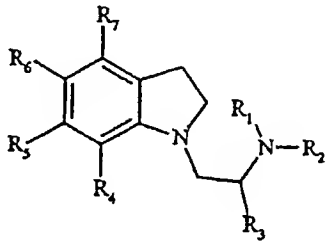
(54) Title: INDOLINE DERIVATIVES AS 5-HT2B AND/OR 5-HT2C RECEPTOR LIGANDS

(57) Abstract



(I)

For use in therapy a chemical compound of formula (I), wherein R_1 to R_3 are independently selected from hydrogen and alkyl; R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen, and pharmaceutically acceptable salts and prodrugs thereof, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea, and especially for the treatment of obesity; chemical compounds of formula (I) other than compounds wherein R_7 is hydroxy.

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INDOLINE DERIVATIVES AS 5-HT2B AND/OR 5-HT2C RECEPTOR LIGANDS

The present invention relates to indoline derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, "*Obesity: Trends and Treatments*", Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

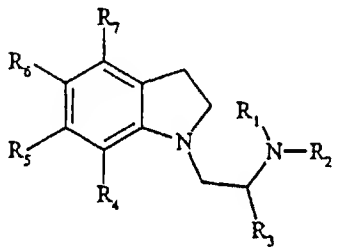
blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, **96**, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, **141**, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, **113**, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, **116**, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, **133**, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, **374**, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, **36**, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethylpyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for $5\text{-}HT_{2B}$ and/or $5\text{-}HT_{2C}$ receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting $5\text{-}HT_{2C}$ receptor ligands, preferably $5\text{-}HT_{2C}$ receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided for use in therapy a chemical compound of formula (I):



(I)

wherein:

R_1 to R_3 are independently selected from hydrogen and alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen,

and pharmaceutically acceptable salts and prodrugs thereof.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to

C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thienyl.

As used herein the term "heterocyclyl" means a saturated 4, 5, 6 or 7-membered ring (preferably a 5 or 6-membered ring) containing 1, 2 or 3 heteroatoms (preferably 1 or 2 heteroatoms) selected from O, S and N (preferably from O and N).

The alkyl, aryl and heterocyclyl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon-containing groups such as

- alkyl,
- aryl,
- arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen-containing groups such as

- haloalkyl (e.g. trifluoromethyl);

oxygen-containing groups such as

- alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
- ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl),
- aldehydes (e.g. carboxaldehyde),
- ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),
- acids (e.g. carboxy, carboxyalkyl),
- acid derivatives such as esters

(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),

amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl),

carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy)

and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen-containing groups such as

amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulfur-containing groups such as

thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl,

morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical.

As used herein the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I).

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2. Preferably, R_1 and R_2 are both hydrogen. In an embodiment of the invention, R_1 is hydrogen and R_2 is substituted or unsubtituted alkyl, preferably lower

alkyl, preferably methyl. Where substituted, the substituent group is preferably an aryl group, preferably phenyl, pyridyl or thienyl.

Preferably, the compounds of formula (I) are selected from compounds in which R_3 is alkyl, preferably lower alkyl, preferably methyl. Where R_3 is alkyl, the carbon atom to which R_3 is attached is an asymmetric carbon atom. It is preferred that this asymmetric carbon atom is in the (*S*)-configuration, wherein the stereochemical assignment is defined with respect to a compound wherein R_3 is an unsubstituted alkyl group.

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, heterocyclyl (including aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, hexahydroazepinyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, tetrahydrothienyl and tetrahydrothiopyranyl), alkoxy (including arylalkoxy), aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is other than hydrogen.

In an embodiment of the invention R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, wherein at least one of R_4 to R_7 is other than hydrogen.

It is preferred that the compounds of formula (I) are selected from compounds in which R_4 is selected from halogen (preferably fluoro) and hydrogen. R_4 is preferably hydrogen.

It is preferred that the compounds of formula (I) are selected from compounds in which R_5 is selected from halogen, alkyl, aryl, alkoxy, alkylthio, monoalkylamino and dialkylamino. Preferably R_5 is selected from halogen, alkyl, alkoxy, alkylthio,

monoalkylamino and dialkylamino, and more preferably from halogen (preferably chloro, bromo and fluoro, more preferably chloro and bromo), alkyl (preferably haloalkyl and more preferably trifluoromethyl), alkoxy (preferably lower alkoxy) and alkylthio (preferably lower alkylthio).

It is preferred that the compounds of formula (I) are selected from compounds in which R_6 is selected from halogen and hydrogen. Preferably R_6 is selected from halogen (preferably fluoro, chloro and bromo, and more preferably fluoro).

It is preferred that the compounds of formula (I) are selected from compounds in which R_7 is hydrogen.

In a preferred embodiment, the compounds of formula (I) are selected from 1-(6-chloro-5-fluoroindolin-1-yl)-2-propylamine, 1-(5,6-difluoroindolin-1-yl)-2-propylamine, 1-(6-bromo-5-fluoroindolin-1-yl)-2-propylamine, 1-(6-bromoindolin-1-yl)-2-propylamine, 1-(6-chloroindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-trifluoromethylindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-methylthioindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-iodoindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-ethylthioindolin-1-yl)-2-propylamine, 1-(-5-fluoro-6-methylindolin-1-yl)-2-propylamine, 1-(6-methylthioindolin-1-yl)-2-propylamine, 1-(6-ethylthioindolin-1-yl)-2-propylamine, 1-(6-trifluoromethylindolin-1-yl)-2-propylamine, 1-(6-methoxyindolin-1-yl)-2-propylamine, 1-(6-propylthioindolin-1-yl)-2-propylamine, 1-(6-isopropylthioindolin-1-yl)-2-propylamine, 2-(6-chloroindolin-1-yl)-1-ethylamine, 2-(6-bromoindolin-1-yl)-1-ethylamine, 1-(5-chloroindolin-1-yl)-2-propylamine, 1-(5-fluoroindolin-1-yl)-2-propylamine and 1-(6-methylindolin-1-yl)-2-propylamine, and particularly the (*S*)-enantiomers thereof.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

In a preferred embodiment of the invention, a compound of formula (I) is in the form of its (*S*)-enantiomer, substantially free of its (*R*)-enantiomer. As used herein, the

term "substantially free of its (*R*)-enantiomer" means that a composition comprising a compound of formula (I) contains a greater proportion of the (*S*)-enantiomer of the compound of formula (I) in relation to the (*R*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention, the term "substantially free of its (*R*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*S*)-enantiomer and 10 % by weight or less of the (*R*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains at least 99 % by weight of the (*S*)-enantiomer and 1 % or less of the (*R*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains 100 % by weight of the (*S*)-enantiomer. The above percentages are based on the total amount of a compound of formula (I) present in the composition.

According to a further aspect of the invention, there is provided a compound of formula (I), *per se*, wherein R_7 is a substituent other than hydroxy. In a preferred embodiment, there is provided a compound of formula (I), *per se*, wherein R_7 is hydrogen.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood,

aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatmcnt (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a method of treatment (including prophylaxis) of a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

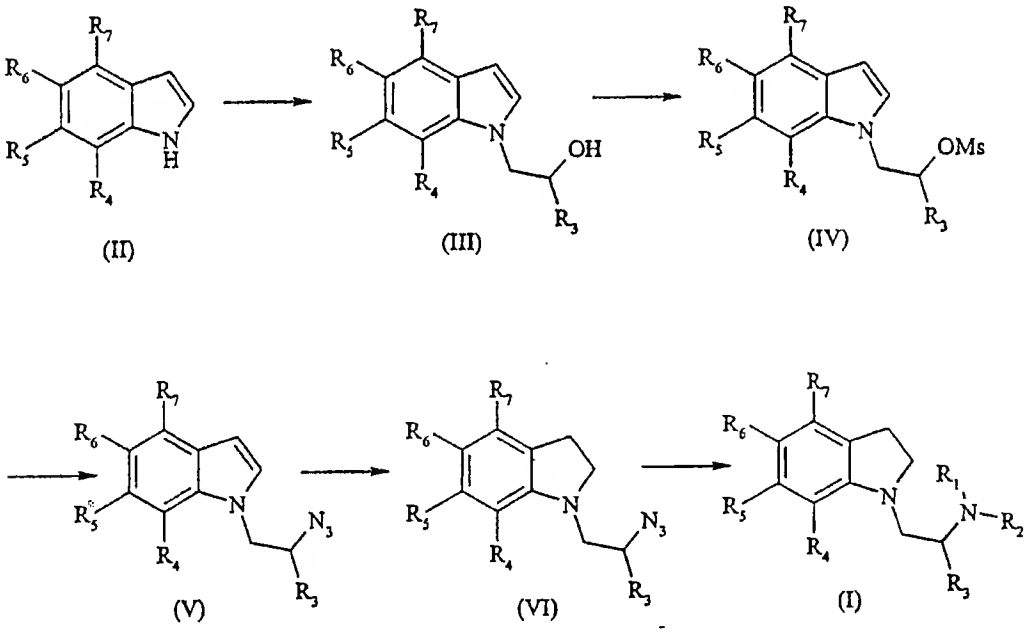
According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I).

Compounds of formula (I) may be prepared according to Reaction Scheme 1 below. R_1 to R_7 are as previously defined. The (indolyl)-alkylethanol (III) may be prepared by reaction of the substituted indole (II) with an alkylene oxide in the presence of a strong base such as sodium hydride in a solvent such as tetrahydrofuran. The corresponding azido derivative (V) can be formed in a two step procedure from the

derivative (III) by formation of the mesylate (IV), obtained by reaction of (III) with methanesulfonyl chloride in the presence of a base such as triethylamine, and subsequent treatment of the mesylate (IV) with sodium azide in a solvent such as dimethyl formamide. The indoline (VI) can then be obtained by reduction of the indole (V) with, for example, sodium cyanoborohydride in acetic acid as solvent. The resultant azidoindoline (VI) can then be reduced to a compound of formula (I) ($R_1 = R_2 = H$) using for example a mixture of zinc powder and nickel chloride hexahydrate in a solvent such as tetrahydrofuran or alternatively using hydrogen over a catalyst such as platinum(IV)oxide in a solvent such as ethanol.

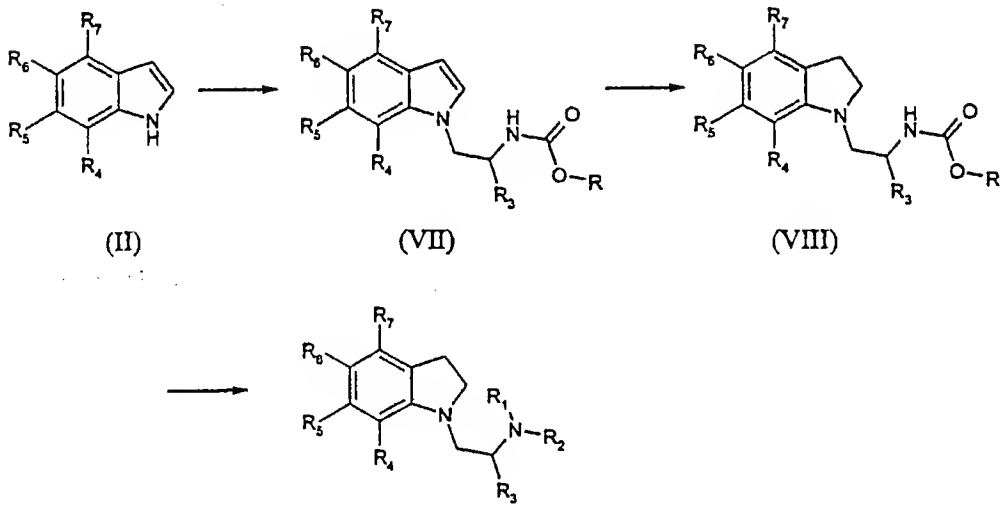
Reaction Scheme 1



Alternatively compounds of the invention may be prepared according to Reaction Scheme 2 below. The carbamate (VII) may be formed by reaction of the indole (II) with a carbamoylethylsulfonate in the presence of a strong base such as potassium hydroxide in a solvent such as methyl sulfoxide. The indoline (VIII) may be obtained by reaction of the indole (VII) with a reducing agent such as sodium cyanoborohydride or a tetra-alkylammonium borohydride. The compounds of formula

(I) ($R_1 = R_2 = H$) may be prepared by deprotection of the amine function of the indoline (VIII).

Reaction Scheme 2



(II) (VII) (VIII) (I)

If, in any of the other processes mentioned herein, the substituent group R_4, R_5, R_6 or R_7 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6 or R_7 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The compounds of formula (I) (R_1 and/or R_2 = alkyl) may be prepared from compounds of formula (I) ($R_1 = R_2 = H$) by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating

the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

The compositions comprising a compound of formula (I) may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of formula (I) may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of formula (I) may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles,

and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of formula (I) are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of formula (I) for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2C} receptor the 5-HT_{2C} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2C} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, **118**, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, **342**, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, **9**, 3482-90.

The thus determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	K_i (2C)	K_i (2B)	K_i (2A)
Example 1	357 nM	113 nM	405 nM
Example 10	55 nM	138 nM	252 nM
Example 12	77 nM	42 nM	1092 nM
Example 13	122 nM	175 nM	461 nM
Example 22	260 nM	92 nM	325 nM
Example 24	235 nM	148 nM	1866 nM
Example 25	63 nM	22 nM	156 nM
Example 26	1156 nM	761 nM	1262 nM
Example 50	61 nM	159 nM	332 nM
Example 51	165 nM	140 nM	1113 nM

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

The thus determined activity of compounds of formula (I) is shown in Table 2.

Table 2

Compound	h5-HT_{2A}		h5-HT_{2C}	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
Example 2	1000	63	100	77
Example 9	5600	52	253	89
Example 10	2215	49	125	62
Example 12	2409	49	230	59
Example 13	386	72	75	74
Example 14	3700	55	2120	71
Example 15	10000	12	4700	14
Example 16	793	52	9	80
Example 17	7500	40	616	76
Example 18	-	7	870	27
Example 19	-	21	3800	34
Example 20	-	17	750	68
Example 22	2567	57	83	87
Example 23	1351	34	354	76
Example 24	3651	33	131	72
Example 25	1244	57	21	81
Example 27	1976	41	233	75
Example 28	1537	63	238	75
Example 29	3167	18	503	68
Example 30	72	88	0.1	95
Example 31	314	72	2	92
Example 32	1516	26	611	63
Example 33	2933	51	257	75
Example 35	10000	30	727	51
Example 37	2733	27	391	69
Example 38	2562	26	320	63
Example 39	260	75	4	87
Example 40	836	64	3	95
Example 41	10000	-	67	83
Example 42	4197	43	54	88

Example 47	10000	5	3545	33
Example 49	10000	5	5478	69
Example 50	4080	25	38	78
Example 51	1893	45	36	88
Example 53	2312	20	266	86
Example 60	10000	-	36	81
Example 61	2184	49	26	68
Example 62	10000	-	329	54
Example 64	10000	30	303	66

3. Efficacy

The efficacy of 5-HT_{2C} agonists was assessed for ability to induce a specific syndrome.

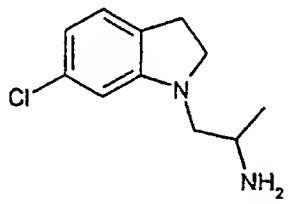
The 5-HT_{2C} syndrome is a rapid screening method to assess the *in vivo* efficacy of 5-HT_{2C} agonists through their ability to induce three specific behaviours in rats. The animals are dosed with either a positive control (mCPP), test compound or vehicle, either sub-cutaneously or p.o.. The animals are observed on an open bench, typically 30, 60 and 180 minutes and the degree of syndrome is assessed over a two minute period on a scale of 0-3 depending on the presence and severity of splayed limbs, hunched posture and retro-pulsion, the three specific behaviours which constitute the syndrome. Data is analysed using Kruskal-Wallis Analysis of Variance followed with appropriate post-hoc tests. All statistical analysis are conducted using Excel version 7.0 (Microsoft Corp.) and Statistica version 5.0 (Statsoft, Inc.).

The thus determined activity of Example 1 indicates that after a dose of 30 mg/kg s.c. the compound maintains significant pharmacological efficacy for at least 180 minutes.

Synthetic Examples

General Method A:

Example 1: (*RS*)-1-(6-Chloroindolin-1-yl)-2-propylamine hydrochloride



Step (a): (*RS*)-1-(6-Chloroindol-1-yl)-2-propanol (1a)

To a stirred suspension of sodium hydride (60%, 1.26 g, 31.6 mmol) in tetrahydrofuran (30 mL) at 0 °C under Ar was added dropwise a solution of 6-chloroindole (4.0 g, 26 mmol) in tetrahydrofuran (30 mL). The mixture was stirred for 1 h and (*RS*)-propylene oxide (3.7 mL, 53 mmol) was added. The mixture was warmed to room temperature, stirred for 48 h and partitioned between aqueous ammonium chloride solution (100 mL) and ether (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; ethyl acetate-hexane (1:9)] to give the product (2.78 g, 50% yield) as a pale yellow oil. Data for the compounds produced using General Method A, step (a) are listed in Table 3.

Step (b): (*RS*)-1-(2-Azidopropyl)-6-chloroindole (1b)

To a stirred solution of (*RS*)-1-(6-chloroindol-1-yl)-2-propanol (2.5 g, 11.9 mmol), dichloromethane (60 mL) and triethylamine (1.8 mL, 13 mmol) at 0 °C was added dropwise methanesulfonyl chloride (1 mL, 13 mmol). The mixture was warmed to room temperature, stirred for 1 h and partitioned between brine (50 mL) and dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (magnesium sulfate) and concentrated *in vacuo* to give a pale yellow

solid (3.3 g), which was added to a stirred mixture of dimethyl formamide (30 mL) and sodium azide (1.1 g, 17 mmol). The mixture was heated to 70 °C, stirred for 16 h, cooled to room temperature and partitioned between brine (50 mL) and ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; ether-hexane (1:9)] to give the product (1.7 g, 63% yield) as a colourless oil. Data for (1b) are included in Table 4 with the data for other compounds produced using General Method A, step (b).

Step (c): *(RS)*-1-(2-Azidopropyl)-6-chloroindoline (1c)

To a stirred solution of (*RS*)-1-(2-azidopropyl)-6-chloroindole (1.5 g, 6.4 mmol) in acetic acid (25 mL) at 5 °C was added portionwise sodium cyanoborohydride (1.2 g, 19 mmol). The mixture was warmed to room temperature, stirred for 16 h and partitioned between ether (100 mL) and aqueous sodium bicarbonate solution (4 x 100 mL). The organic layer was washed (brine), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2:ethyl acetate-hexane (1:9)] to give the product (1.39 g, 92% yield) as a pale yellow oil. Data for (1c) are included in Table 5 with the data for other compounds produced using General Method A, step (c).

Step (d): *(RS)*-1-(6-Chloroindolin-1-yl)-2-propylamine hydrochloride (1)

To a stirred solution of (*RS*)-1-(2-azidopropyl)-6-chloroindoline (0.92 g, 1.8 mmol) in tetrahydrofuran (70 mL) at 0 °C under Ar was added portionwise a mixture of Zinc powder (1.3 g, 20 mmol) and nickel chloride hexahydrate (6.8 g, 28 mmol). The mixture was warmed to room temperature, stirred for 16 h, and partitioned between water (50 mL) and ethyl acetate (3 x 30 mL). The combined organic extracts were washed (brine), dried (magnesium sulfate) and concentrated *in vacuo* to give a pale brown oil. The oil was dissolved in a mixture of ether (10 mL) and dichloromethane (20 mL) and the solution was cooled to 0 °C. Ethereal hydrogen chloride solution (1.0 M, 3.9 mL, 3.9 mmol) was added dropwise and the mixture stirred at room temperature for 10 min. The mixture was concentrated *in vacuo* and recrystallised (2-propanol) to

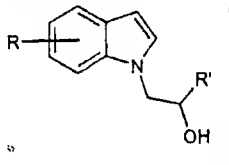
give the product (0.42 g, 38% yield) as a pale pink solid. Data for (1) are included in Table 6 with the data for other compounds produced using General Method A, step (d).

Alternative Step (d): *(RS)*-1-(6-Methoxyindolin-1-yl)-2-propylamine hydrochloride (2)

A mixture of (*RS*)-1-(2-azidopropyl)-6-methoxyindoline (0.27 g, 1.1 mmol), ethanol (10 mL) and platinum(IV)oxide (0.01 g, 0.04 mmol) was stirred under hydrogen for 12 h. The mixture was filtered through a pad of Celite® and concentrated *in vacuo* to give a pale yellow oil, which was dissolved in ether (5 mL) and cooled to 0 °C. Ethereal hydrogen chloride solution (1.0 M, 1.1 mL, 1.1 mmol) was added dropwise and the mixture was was concentrated *in vacuo* and recrystallised (2-propanol) to give the product (0.18 g, 64%) as a pale blue solid. Data for (2) are included in Table 6 with the data for other compounds produced using General Method A, step (d).

The compounds shown in Tables 3, 4, 5 and 6 were prepared using General Method A from (*RS*)-propylene oxide, (*R*)-propylene oxide, (*RS*)-1,2-epoxybutane and fumaric acid as appropriate.

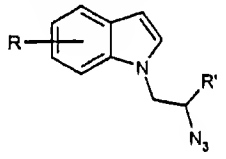
Table 3: Indoles prepared using General Method A, step (a)

No		Data
1a	R = 6-Cl R' = Me	IR ν_{max} (film)/cm^{-1} 3387, 2972, 2931, 1711, 1608, 1506, 1465, 1396, 1377, 1339, 1320, 1243, 1200, 1139, 1091, 1065, 938, 908, 898, 839, 805, 721, 673, 605 and 492; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6 Hz), 3.98 (1H, dd, *J* 8, 14.5 Hz), 4.12 (1H, dd, *J* 3.5, 14.5 Hz), 4.19 (2H, m), 6.49 (1H, d, *J* 3.5 Hz), 7.07 (1H, dd, *J*, 2, 8.5 Hz), 7.13 (1H, d, *J* 3.5 Hz), 7.36 (1H, d, *J* 2 Hz), 7.52 (1H, d, *J* 8.5 Hz).
2a	R = 6-OMe R' = Me	NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6 Hz), 3.86 (3H, s), 3.96 (1H, dd, *J* 14 and 8 Hz), 4.08 (1H, dd, *J* 14 and 4 Hz), 4.15 (1H, m), 6.43 (1H, d, *J* 3 Hz), 6.82 (2H, m), 7.01

		(1H, d, *J* 3 Hz), 8.5 (1H, d, *J* 8.5 Hz).
3a	R = 6-Me R' = Me	IR ν_{max} (film)/cm^{-1} 3406, 1621, 1510, 1469, 937, 802 and 718; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6 Hz), 2.47 (3H, s), 3.99 (1H, m), 4.19 (2H, m), 6.45 (1H, d, *J* 2.5 Hz), 6.95 (1H, d, *J* 8 Hz), 7.04 (1H, d, *J* 2.5 Hz), 7.14 (1H, m) and 7.50 (1H, d, *J* 8 Hz)
4a	R = 5-OBn R' = Me	mp 72 °C. Found: C, 76.81; H, 6.79; N, 5.00%. $C_{18}H_{19}NO_2$ requires : C, 76.84; H, 6.81; N, 4.98 %.
5a	R = 4-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 3412, 1578, 1496, 1453, 1368, 1255, 1056 and 736; NMR δ_H (400 MHz, $CDCl_3$), 1.23 (3H, d, *J* 6.5 Hz), 1.78 (1H, br s), 3.91-3.99 (1H, m), 4.04-4.18 (2H, m), 5.23 (2H, s), 6.59, (1H, d, *J* 8 Hz), 6.70 (1H, d, *J* 4 Hz), 6.99, (1H, d, *J*, 8.5 Hz), 7.05 (1H, d, *J* 3.5 Hz), 7.12, (1H, t, *J* 7.5 Hz), 7.28-7.34 (1H, m), 7.35-7.47 (2H, m) and 7.46-7.52 (2H, m).
6a	R = 6-Cl R' = Et	IR ν_{max} (film)/cm^{-1} 3396, 2967, 1608, 1464, 1319, 901 and 720; NMR δ_H (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.5 Hz), 1.37-1.60 (2H, m), 1.82-1.88 (1H, brs), 3.76-3.85 (1H, m), 3.87-3.97 (1H, m), 4.15 (1H, dd, *J* 14.5, 3.5 Hz), 6.41-6.48 (1H, m), 7.02-7.13 (2H, m), 7.31-7.35 (1H, m) and 7.46-7.53 (1H, m)
7a	R = 6-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 3419, 1622, 1488, 1466, 1454, 1377, 1316, 1262, 1191, 1095, 1025 and 809; (400 MHz, $CDCl_3$), 1.23 (3H, d, *J* 6.5), 3.9-3.98 (1H, m), 4.03-4.19 (2H, m), 5.12 (2H, s), 6.42-6.46 (1H, m), 6.85-6.92 (2H, m), 7.02 (1H, d, *J* 3 Hz), 7.29-7.35 (1H, m), 7.36-7.42 (2H, m) and 7.44-7.52 (3H, m)

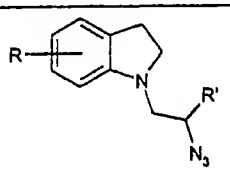
8a	R = 6-CF_3 R' = Me	IR ν_{max} (film)/cm^{-1} 3353, 3285, 1468, 1354, 1311, 1250, 1154, 1092, 1054 and 813; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, J 6.5 Hz), 4.01-4.08 (1H, m), 4.13-4.22 (1H, m), 6.55 (1H, d, *J* 3 Hz), 7.27 (1H, d, *J* 3 Hz), 7.34 (1H, d, *J* 8 Hz), 7.63 (1H, s) and 7.68 (1H, d, *J* 8 Hz)
9a	R = 6-F R' = Me (*R*)	IR ν_{max} (film)/cm^{-1} 3384, 1621, 1488, 949 and 718; NMR δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6 Hz), 3.88 (1H, dd, *J* 7.5 Hz), 4.04-4.06 (1H, m), 4.06-4.09 (1H, m), 6.43 (1H, d, *J* 3 Hz), 6.82-6.87 (1H, m), 7.01 (1H, dd, *J* 9.5, 2.5 Hz), 7.05 (1H, d, *J* 3 Hz) and 7.49 (1H, dd, *J* 8.5, 5 Hz)

Table 4: Indoles prepared using General Method A, step (b)

No		Data
1b	R = 6-Cl R' = Me	IR ν_{max} (film)/cm^{-1} 2934, 2117, 1607, 1464, 806, 720 and 603; NMR δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5 Hz), 3.90 (1H, m), 4.05 (2H, m), 6.52 (1H, m), 7.10 (2H, m), 7.31 (1H, m) and 7.53 (1H, d, *J* 8 Hz)
2b	R = 6-OMe R' = Me	NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6 Hz), 3.86 (3H, s), 3.96 (1H, dd, *J* 14 and 8 Hz), 4.08 (1H, dd, *J* 14 and 4 Hz), 4.15 (1H, m), 6.43 (1H, d, *J* 3 Hz), 6.82 (2H, m), 7.01 (1H, d, *J* 3 Hz), 8.5 (1H, d, *J* 8.5 Hz)
3b	R = 6-Me R' = Me	IR ν_{max} (film)/cm^{-1} 2117, 1621, 1467, 1259, 803 and 717; NMR δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.5 Hz), 2.50 (3H, s), 3.96 (1H, m), 4.09 (2H, m), 6.49 (1H, d, *J* 3 Hz), 6.97 (1H. d, *J* 8 Hz), 7.04 (1H, d, *J* 3 Hz), 7.11 (1H, s) and 7.53 (1H, d, *J* 8 Hz).

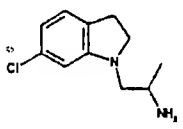
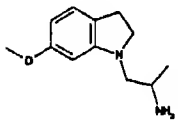
4b	R = 5-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 2975, 2932, 2870, 2118, 1726, 1621, 1576, 1485, 1453, 1382, 1258, 1238, 1154, 1025, 847, 790, 720, 624 and 554; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, J 6.5 Hz) 3.88 (1H, m) 4.05 (2H, m) 5.08 (2H, s) 6.43 (1H, d, J 4 Hz) 6.95 (1H, dd, J 2.5, 8.5 Hz) 7.06 (1H, d, J 3 Hz) 7.16 (1H, d, J 2.5 Hz) 7.22 (1H, m) 7.30 (1H, t, J 7 Hz) 7.37 (2H, t, J 7 Hz) 7.46 (2H, d, J 7 Hz).
5b	R = 4-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 2117, 1579, 1496, 1453, 1369, 1256, 1056 and 736; NMR δ_H (400 MHz, $CDCl_3$), 1.26 (3H, d, *J* 6.5 Hz), 3.91 (1H, m), 4.07 (2H, d, *J* 6 Hz), 5.22 (2H, s), 6.59 (1H, d, *J* 7.5 Hz), 6.7 (1H, d, *J* 4 Hz), 6.95 (1H, d, *J* 8 Hz), 7.01, (1H, d, *J* 3 Hz), 7.12 (1H, t, *J* 7.5 Hz), 7.29-7.34 (1H, m), 7.36-7.42 (2H, m) and 7.47-7.53 (2H, m)
6b	R = 6-Cl R' = Et	IR ν_{max} (film)/cm^{-1} 2970, 2935, 2099, 1464, 901, 806 and 719 ; NMR δ_H (400 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.5 Hz), 1.42-1.71 (2H, m), 3.56-3.68 (1H, m), 3.90-4.0 (1H, m), 4.07-4.16 (1H, m), 6.45-6.54 (1H, m), 7.03-7.12 (2H, m), 7.28-7.31 (1H, m) and 7.48-7.56 (1H, m)
7b	R = 6-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 2117, 1622, 1488, 1264, 1194, 1025 and 809; (400 MHz, $CDCl_3$), 1.24 (3H, d, *J* 6.5 Hz), 3.85 (1H, m), 4.01 (2H, d, *J* 6.5 Hz), 5.13 (2H, s), 6.44-6.47 (1H, m), 6.82-6.91 (2H, m), 6.99 (1H, d, 3 Hz), 7.29-7.35 (1H, m), 7.36-7.42 (2H, m) and 7.45-7.53 (3H, m)
8b	R = 6-CF_3 R' = Me	IR ν_{max} (film)/cm^{-1} 2117, 1617, 1455, 1318 and 1118; NMR δ_H (400 MHz, $CDCl_3$)1.31 (3H, d, *J* 7.5 Hz), 3.01-3.07 (2H, m), 3.10-3.15 (2H, m), 3.49-3.59 (2H, m), 3.74-3.78 (1H, m), 6.58 (1H, s), 6.90-6.92 (2H, m) and 7.10-7.12 (1H, m)
9b	R = 6-F R' = Me, (*S*)	IR ν_{max} (film)/cm^{-1} 2119, 1621, 1468, 1255, 948 and 717; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6 Hz), 3.87-4.03 (3H, m), 6.48 (1H, d, *J* 3 Hz), 6.82-6.86 (1H, m), 6.98 (1H, dd, *J* 9.5, 2.5 Hz), 7.05 (1H, d, *J* 3 Hz) and 7.51 (1H, dd, *J* 8.5, 5.5 Hz)

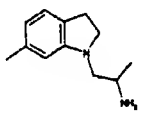
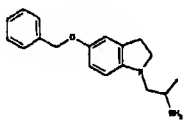
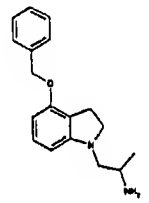
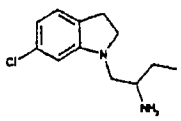
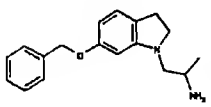
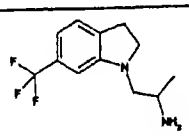
Table 5: Indolines prepared using General Method A, step (c)

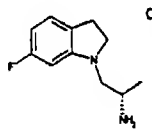
No		Data
1c	R = 6-Cl R' = Me	IR ν_{max} (film)/cm^{-1} 2642, 2115, 1606, 1493, 1271, 1010, 879 and 589; NMR δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.5 Hz), 2.96 (2H, m), 3.07 (2H, m), 3.52 (2H, m), 3.76 (1H, m), 6.39 (1H, d, *J* 2 Hz), 6.60 (1H, dd, *J* 7.5 and 2 Hz) and 6.94 (1H, d, *J* 7.5 Hz).
2c	R = 6-OMe R' = Me	IR ν_{max} (film)/cm^{-1} 2115, 1621, 1498, 1211, 820 and 631; NMR δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5 Hz), 2.93 (2H, m), 3.16 (2H, m), 3.46 (2H, m), 3.76 (1H, m), 6.04 (1H, d, *J* 2 Hz), 6.18 (1H, dd, *J* 8 and 2 Hz) and 6.95 (1H, d, *J* 8 Hz)
3c	R = 6-Me R' = Me	IR ν_{max} (film)/cm^{-1} 2115, 1614, 1647, 1020 and 796; NMR δH (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.5 Hz), 2.29 (3H, s), 2.98 (2H, m), 3.06 (1H, m), 3.16 (1H, m), 3.50 (2H, m), 3.78 (1H, m), 6.29 (1H, m), 6.50 (1H, d, *J* 7 Hz) and 6.97 (1H, d, *J* 7 Hz).
5c	R = 4-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 2114, 1615, 1464, 1228, 1062 and 754; NMR δ_H (400 MHz, $CDCl_3$), 1.29, (3H, d, *J* 6.5 Hz), 2.98-3.09 (3H, m), 3.11-3.18 (1H, m), 3.42-3.56 (2H, m), 3.75 (1H, m), 5.08 (2H, s), 6.16 (1H, d, *J* 8 Hz), 6.33 (1H, d, *J* 8 Hz), 6.97-7.06 (1H, m), 7.28-7.33 (1H, m) and 7.34-7.44 (4H, m)
6c	R = 6-Cl R' = Et	IR ν_{max} (film)/cm^{-1} 2968, 2934, 2097, 1606, 1493, 1271 and 883; NMR δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.5 Hz), 1.48-1.66 (2H, m), 2.93-2.97 (2H, m), 3.07-3.14 (2H, m), 3.46-3.56 (3H, m), 6.36-6.40 (1H, m), 6.55-6.63 (1H, m) and 6.89-6.99 (1H, m)

7c	R = 6-OBn R' = Me	IR ν_{max} (film)/cm^{-1} 2115, 1620, 1498, 1285, 1191, 1091, 1025 and 735; (400 MHz, $CDCl_3$), 1.27 (3H, d, *J* 6.5 Hz), 2.94 (2H, t, *J* 8 Hz), 3.06 (2H, m), 3.48 (2H, m), 3.74 (1H, m), 5.02 (2H, s), 6.12 (1H, d, *J* 2 Hz), 6.23-6.28 (1H, m), 6.91-6.97 (1H, d, 8 Hz) and 7.27-7.46 (5H, m)
8c	R = 6-CF_3 R' = Me	IR ν_{max} (film)/cm^{-1} 3373, 2976, 2935, 2847, 2117, 1617, 1318 and 663; NMR δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 7 Hz) 2.93-3.20 (4H, m) 3.45-3.55 (2H, m) 3.71-3.75 (1H, m) 6.34-6.44 (1H, m) 6.80-6.85 (1H, m) and 7.10-7.20 (1H, m)
9c	R = 6-F R' = Me, (*S*)	IR ν_{max} (film)/cm^{-1} 2116, 1619, 1496, 1275, 822 and 612; NMR δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5 Hz) 2.93-2.95 (2H, m), 3.04-3.06 (2H, m), 3.51-3.53 (2H, m), 3.72-3.74 (1H, m), 6.13 (1H, dd, *J* 10, 2.5 Hz), 6.29-6.31 (1H, m) and 6.93-6.95 (1H, m)

Table 6: **Examples 1-9.** Indolines prepared using General Method A, step (d)

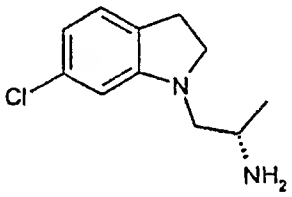
No	Structure	Data
1		HCl. mp 262 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1589, 1489, 1462, 882 and 840; NMR δ_H (400 Mz, DMSO-d_6) 1.28 (3H, d, *J* 6.5 Hz), 2.54 (2H, m), 2.94 (2H, m), 3.08 (1H, m), 3.34 (2H, m), 3.46 (1H, m), 3.58 (1H, m), 6.64 (2H, m), 7.64 (1H, d, *J* 7.5 Hz) and 8.0 (3H, br).
2		HCl. mp 142-143 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1619, 1496, 1464, 1098, 831 and 788; NMR δ_H (400 MHz, DMSO-d_6) 1.25 (3H, d, *J* 6.5 Hz), 2.50 (3H, s), 3.02 (1H, m), 3.08 (2H, m), 3.26 (2H, m), 3.40 (1H, m), 3.49 (2H, m), 6.24 (1H, m), 6.24 (1H, m), 6.92 (1H, d, *J* 8 Hz) and 8.05 (3H, br).

3		HCl. mp 178-179 °C, IR ν_{max} (Nujol)/cm^{-1} 3345, 2925, 1613, 1494, 1460, 1270, 1186 and 796; NMR δ_H (400 MHz, DMSO-d_6) 1.25 (3H, d, *J* 6.5 Hz), 2.19 (3H, s), 2.87 (2H, m), 2.99 (1H, dd, *J* 14 and 5 Hz), 3.22 (2H, m), 3.43 (2H, m), 6.43 (2H, m), 6.92 (1H, d, *J* 8 Hz) and 8.05 (3H, br).
4		Fumarate mp 143-4 °C; Found: C, 65.69; H, 6.53; N, 6.95% $C_{18}H_{22}N_2O.C_4H_4O_4.0.25\ H_2O$ requires C, 65.57; H, 6.63; N, 6.95%.
5		HCl. mp 188-190 °C; Found: C, 67.79; H, 7.35; N, 8.70%. $C_{18}H_{22}N_2O.HCl$ requires: C, 67.81; H, 7.27; N, 8.78%; IR ν_{max} (Nujol)/cm^{-1} 1614, 1460, 1377, 1257, 1237, 1064 and 758; NMR δ_H (400 MHz, DMSO-d_6), 1.26 (3H, d, *J* 6.5 Hz), 2.79-2.96 (2H, m), 2.97-3.05 (1H, m), 3.23-3.34 (2H, m), 3.35-3.43 (1H, m), 3.45-3.54 (2H, m), 5.09 (2H, m), 6.29 (1H, d, *J* 7.5 Hz), 6.39 (1H, d, *J* 7.5 Hz), 7.28-7.34 (1H, m), 7.39-7.44 (4H, m) and 8.22 (3H, br s).
6		HCl. mp 188-192 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.75 (3H, t, *J* 7.5 Hz), 1.27-1.44 (2H, m), 2.57-2.68 (1H, m), 2.77-2.89 (1H, m), 2.88-3.12 (4H, m), 3.23-3.34 (1H, m), 6.30-6.38 (2H, m) and 6.71-6.80 (1H, m).
7		mp 178-179 °C;. Found: C, 70.21; H, 7.12; N, 8.00%. $C_{18}H_{22}N_2O.0.5\ C_4H_4O_4$ requires: C, 75.56; H, 7.11; N, 8.23%; IR ν_{max} (Nujol)/cm^{-1} 1621, 1545, 1456, 1349, 1181, 1024, 732 and 667; ; (400 MHz, d_6DMSO), 1.15 (3H, d, *J* 6.5 Hz), 2.78-2.87 (2H, m), 2.89-2.99 (1H, m), 3.09-3.17 (1H, m), 3.22-3.32 (2H, m), 3.4-3.48 (1H, m), 5.01 (2H, s), 6.2 (1H, d, *J* 6.5), 6.24 (1H, m), 6.39 (1H, s), 6.89 (1H, d, *J* 8 Hz) and 7.27-7.45 (5H, m)
8		Fumarate. mp 154-8 °C; IR ν_{max} (Nujol)/cm^{-1} 1618, 1457, 1378, 1318, 1162, 1118 and 1060.

9		Fumarate. mp 150-153 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.20 (3H, d, *J* 6.0 Hz), 2.86-2.88 (1H, m), 3.01 (1H, dd, *J* 14, 5.5 Hz), 3.23-3.25 (1H, m), 3.34-3.36 (2H, m), 3.52-3.56 (1H, m), 6.30-6.32 (1H, m), 6.40-6.45 (1H, m) and 6.97-6.99 (1H, m).

General Method B:

Example 10: (*S*)-1-(6-Chloroindolin-1-yl)-2-propylamine fumarate



Step (a): (*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-chloroindole (10a)

6-Chloroindole (1.5 g, 10 mmol) was added portionwise to a stirred suspension of powdered potassium hydroxide (2.24 g, 40 mmol) in methyl sulfoxide (25 mL). The mixture was warmed to 35 °C and stirred for 30 min. A solution of (*S*)-2-(tert-butoxycarbonylamino)propane methanesulfonate (6.3 g, 25 mmol) in methyl sulfoxide (10 mL) was added over 2 h. The mixture was stirred for 20 h and partitioned between water (50 mL) and ether (3 x 30 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (6:1)] to give the product (0.75 g, 24% yield) as a pink solid. Data for (10a) are included in Table 7 with the data for other compounds produced using General Method B, step (a).

Step (b): (*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-chloroindoline (10b)

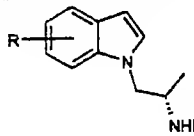
To a stirred solution of (S)-1-[2-(tert-butoxycarbonylamino)propyl]-6-chloroindole (0.7 g, 2.3 mmol) in acetic acid (15 mL) was added portionwise sodium cyanoborohydride (0.43 g, 6.9 mmol). The mixture was stirred for 16 h and partitioned between ether (40 mL) and saturated aqueous sodium bicarbonate solution (3 x 50 mL). The organic layer was washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (6:1)] to give the product (0.57 g, 80%) as a white solid. Data for (10b) are included in Table 8 with the data for other compounds produced using General Method B, step (b).

Step (c): (*S*)-1-(6-Chloroindolin-1-yl)-2-propylamine fumarate (10)

To a stirred solution of (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-chloroindoline (0.5 g, 1.6 mmol) in dichloromethane (5 mL) was added dropwise trifluoroacetic acid (5 mL). The mixture was stirred for 1 h and partitioned between aqueous sodium hydroxide solution (2 M, 50 mL) and dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate) and concentrated *in vacuo* to give a pale yellow oil. The oil was dissolved in 2-propanol (5 mL) and the solution was heated to boiling then fumaric acid (0.18 g, 1.6 mmol) was added. The mixture was cooled to room temperature and filtered. The filter-cake was dried *in vacuo* to give the product (0.39 g, 75%) as a white solid. Data for (10) is included in Table 9 with the data for other compounds produced using General Method B, step (c).

The compounds shown in Tables 7, 8 and 9 were prepared using General Method B from either commercially available indoles or from indoles synthesised according to the methods described after Table 9 using (*RS*)-2-(tert-butoxycarbonylamino)propane methanesulfonate, (*S*)-2-(tert-butoxycarbonylamino)propane methanesulfonate or (*R*)-2-(tert-butoxycarbonylamino)propane methanesulfonate as appropriate.

Table 7: Indoles prepared using General Method B, step (a)

No		Data
10a	6-Cl (*S*)	mp 144-146 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.5 Hz), 1.45 (9H, s), 4.02-4.49 (4H, m), 6.51 (1H, d, *J* 3 Hz), 7.06-7.12 (2H, m), 7.42 (1H, brs) and 7.54 (1H, d, *J* 9 Hz).
11a	7-OBn (*RS*)	IR ν_{max} (Nujol)/cm^{-1} 3366, 1684, 1526, 1455, 1373, 1319, 1175, 1058 and 717; NMR δ_H (400 MHz, $CDCl_3$) 0.871 (3H, br s), 0.93-1.36 (9H, m), 3.84-4.01 (1H, m), 4.21-4.44 (2H, m), 4.69-4.84 (1H, m), 5.18 (2H, br s), 6.43 (1H, br s), 6.72 (1H, d, *J* 7.5 Hz), 7.22 (1H, d, *J* 7.5 Hz) and 7.34-7.53 (5H, m).
12a	6-Br (*S*)	IR ν_{max} (neat)/cm^{-1} 2941, 1739, 1574, 1498, 1270, 1033 and 828; NMR δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7 Hz), 1.43 (9H, s), 3.68-3.74 (1H, m), 4.0-4.18 (2H, m), 4.42 (1H, brs), 6.48 (1H, d, *J* 3 Hz), 7.04 (d, *J* 3 hz), 7.19 (1H, dd, *J* 8.5, 1 Hz), 7.46 (d, *J* 8.5 Hz) and 7.54 (1H, brs).
13a	6-OMe (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1458, 1363, 1220, 1051, 812 and 625; NMR δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7 Hz), 1.50 (9H, s), 3.93 (3H, s), 3.98-4.10 (3H, m), 4.52 (1H, brs), 6.41-6.45 (1H, m), 6.74-6.83 (1H, m), 6.94-6.99 (1H, m), and 7.46-7.53 (1H, m).
14a	5-Me, 6-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1681, 1531, 1463, 1165, 1061, 974 and 645; NMR δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6 Hz), 1.44 (9H, s), 2.43 (3H, s), 4.01-4.16 (3H, m), 4.38 (1H, brs), 6.41 (1H, d, *J* 3 Hz), 7.01 (1H, d, *J* 3 Hz), 7.40 (1H, s) and 7.44 (1H, s).
15a	5-F, 6-Cl (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1680, 1532, 1461, 1168, 815 and 715; NMR δ_H (400 MHz, $CDCl_3$) 1.1 (3H, d, *J* 8 Hz), 1.42 (9H, s), 4.01-4.13 (3H, m), 4.36 (1H, brs), 6.43 (d, *J* 3 Hz), 7.07

		(1H, d, *J* 3 Hz), 7.30 (1H, d, *J* 6 Hz) and 7.40 (1H, d, *J* 6 Hz).
16a	5-F, 6-Cl (*S*)	IR ν_{max} (film)/cm^{-1} 1680, 1531, 1370, 1064 and 815; NMR δ_H (400 MHz, $CDCl_3$) 1.1 (3H, d, *J* 8 Hz), 1.42 (9H, s), 4.01-4.13 (3H, m), 4.36 (1H, brs), 6.43 (d, *J* 3 Hz), 7.07 (1H, d, *J* 3 Hz), 7.30 (1H, d, *J* 6 Hz) and 7.40 (1H, d, *J* 6 Hz).
17a	5-F, 7-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1528, 1459, 1060 and 717; NMR δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6 Hz), 1.28 (9H, s), 3.97-4.07 (1H, m), 4.35-4.56 (3H, m), 6.44 (1H, d, *J* 3 Hz), 6.94 (1H, dd, *J* 9, 2.5 Hz), 7.07 (1H, brs) and 7.14 (1H, dd, *J* 9, 2.5 Hz).
18a	6-Br (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1533, 1462, 1173, 1062, 799 and 718; NMR δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7 Hz), 1.43 (9H, s), 4.0-4.15 (3H, m), 4.39 (1H, brs), 6.48 (1H, d, *J* 3 Hz), 7.04 (1H, d, *J* 3 Hz), 7.20 (1H, dd, *J* 8.5, 2 Hz), 7.46 (1H, d, *J* 8.5 Hz) and 7.54 (1H, brs).
19a	7-Br (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1682, 1528, 1453, 1316, 1173, 777 and 713; NMR δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7 Hz), 1.29 (9H, s), 4.40-4.48 (1H, m), 4.50-4.69 (3H, m), 6.52 (1H, d, *J* 3 Hz), 6.95 (1H, t, *J* 8 Hz), 7.11 (1H, brs), 7.36-7.39 (1H, m) and 7.56-7.58 (1H, m).
20a	7-Br (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1528, 1453, 1316, 1173, 1059, 777 and 713; NMR δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7 Hz), 1.28 (9H, s), 3.94-4.71 (4H, m), 6.47 (1H, d, *J* 3 Hz), 6.89 (1H, t, *J* 7 Hz), 7.06 (1H, brs), 7.32 (1H, dd *J* 7.5, 1 Hz) and 7.52 (1H, dd, *J* 8, 1 Hz).
21a	6,7-dichloro (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1684, 1526, 1458, 1317, 1061, 800 and 720; NMR δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5 Hz), 1.34 (9H, s), 4.43-4.51 (1H, m), 4.58-4.65 (4H, m), 6.50 (1H, d, *J* 3 Hz), 7.09 (1H, brs), 7.19 (1H, d, *J* 8.5 Hz)

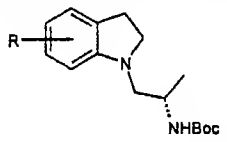
		and 7.44 (1H, d, *J* 8.5 Hz).
23a	6,7-dichloro (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1685, 1526, 1317, 1179, 1061, 800 and 719; NMR δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 7 Hz), 1.89 (9H, s), 3.92-4.11 (2H, m), 4.35-4.56 (1H, m), 4.58 (1H, brs), 6.45 (1H, d, *J* 3 hz), 7.04 (1H, brs), 7.14 (1H, d, *J* 8.5 Hz) and 7.38 (1H, d, *J* 8.5 Hz).
24a	6-CF_3 (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1684, 1533, 1348, 1109, 812 and 622; NMR δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.5 Hz), 1.33 (9H, s), 3.99-4.19 (3H, m), 4.39 (1H, brs), 6.52 (1H, d, *J* 3 Hz), 7.17 (1H, d, *J* 3Hz), 7.28 (1H, d, *J* 9 Hz) and 7.61-7.64 (1H, m).
25a	5-F, 6-Br (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1679, 1533, 1479, 1165, 1064, 812 and 663; NMR δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5 Hz), 1.42 (9H, s), 3.99-4.08 (1H, m), 4.10-4.18 (2H, m), 4.39 (1H, brs), 6.45 (1H, d, *J* 3 Hz), 7.1 (1H, d, *J* 3 Hz), 7.36 (1H, d, *J* 9 Hz) and 7.56 (1H, d, *J* 5.5 Hz).
26a	6-CF_3 (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1533, 1461, 1308, 1109, 812 and 662; NMR δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.5 Hz), 1.39 (9H, s), 4.06-4.12 (3H, m), 4.39 (1H, brs), 6.58 (1H, d, *J* 3 Hz), 7.23 (1H, d, *J* 3 Hz), 7.34 (1H, d, *J* 8 Hz) and 7.70 (1H, d, *J* 8 Hz).
27a	6-Cl, 7-F (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1687, 1615, 1197, 1080 and 543; NMR δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.5 hz), 1.31 (9H, s), 3.99-4.08 (1H, m), 4.28-4.43 (3H, m), 6.46-6.48 (1H, m), 7.01 (1H, dd, J 6.5 Hz), 7.04 (1H, brs) and 7.24-7.26 (1H, m).
28a	5-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1516, 1174, 1076 and 716; NMR δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.5 Hz), 1.48 (9H, s), 4.04-4.17 (1H, m), 4.26-4.35 (2H, m), 4.43 (1H, brs), 6.49 (1H, d, *J* 3 Hz), 7.13 (1H, d, *J* 3 Hz), 7.21 (1H,

		dd, *J* 8, 2 Hz), 7.41 (1H, d, *J* 8 Hz) and 7.63 (1H, d, *J* 2 Hz).
29a	5-F (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1684, 1515, 1488, 1364, 1172, 1075 and 718; NMR δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 7 Hz), 1.49 (9H, s), 4.06-4.16 (2H, m), 4.27-4.36 (1H, m), 4.45 (1H, brs), 6.51 (1H, d, *J* 3Hz), 7.0 (1H, td, *J* 8.5, 2.5 Hz), 7.15 (1H, d, *J* 3 Hz), 7.28-7.32 (2H, m) and 7.41 (1H, brs).
30a	5-F, 6-MeS (*S*)	mp 119-124 °C; IR ν_{max} (Nujol)/cm^{-1} 3361, 2924, 2854, 1678, 1531, 1475, 1164 and 1064; NMR δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.0 Hz), 1.43 (9H, s), 2.52 (3H, s), 3.98-4.10 (2H, m), 4.18-4.33 (1H, m), 4.34-4.48 (1H, m), 6.42-6.44 (1H, m), 7.07 (1H, d, *J* 3.0 Hz), 7.24-7.29 (1H, d, *J* 10.0 Hz), 7.43-7.50 (1H, m).
31a	5-F, 6-EtS (*S*)	mp 133 °C; IR ν_{max} (Nujol)/cm^{-1} 3368, 2925, 2854, 1682, 1529, 1474, 1251, 1163 and 1061; NMR δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5 Hz), 1.27 (3H, t, *J* 7.5), 1.42 (9H, s), 2.94 (2H, q, *J* 7.5 Hz)), 3.98-4.13 (2H, m), 4.15-4.29 (1H, m), 4.32-4.46 (1H, m), 6.43-6.44 (1H, m), 7.09 (1H, d, *J* 3.0 Hz), 7.24-7.30 (1H, m), 7.47-7.53 (1H, m).
32a	4-Me (*S*)	mp 65-66 °C; IR ν_{max} (Nujol)/cm^{-1} ; NMR δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 2.54 (3H, s), 4.07 (2H, m), 4.26 (1H, m), 6.51 (1H, d, *J* 3 Hz), 6.90 (1H, dd, *J* 1, 7 Hz), 7.05 (1H, d, J 3 Hz), 7.11 (1H, dd, *J* 7, 8 Hz), 7.27 (1H, d, *J* 8 Hz).
33a	5-Br (*S*)	mp 115-116 °C; Found: C, 54.43; H, 5.94; N, 7.85%. $C_{16}H_{21}N_2BrO_2$ requires C, 54.40; H, 5.99; N, 7.93%; NMR δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.5 Hz), 1.42 (9H, s), 4.03 (2H, m), 4.23 (1H, m), 6.42 (1H, d, *J* 3 Hz), 7.04 (1H, d, *J* 3 Hz), 7.26 (1H, d, *J* 1.5 Hz), 7.29 (1H, m), 7.71 (1H, t, *J* 1.5 Hz).

34a	5,6-di-OMe (*S*)	IR ν_{max} (Nujol)/cm^{-1} ; 3358, 2925, 2854, 1680, 1514, 1488, 1457, 1365, 1293, 1238, 1170, 1147, 1078, 1028 and 840; NMR δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 3.91 (3H, s), 3.96 (3H, s), 3.98 (1H, m), 4.06 (1H, m), 4.25 (1H, m), 6.38 (1H, d, *J* 3 Hz), 6.93 (1H, d, *J* 3 Hz), 7.04 (1H, brs.), 7.06 (1H, s).
35a	4-F (*S*)	mp 100-101 °C; Found: C, 65.23; H, 7.05; N, 9.47%. $C_{16}H_{22}N_2FO_2$ requires C, 65.73; N, 7.24; N, 9.58 %; NMR δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 4.07 (2H, m), 4.26 (1H, m), 6.58 (1H, d, *J* 3 Hz), 6.76 (1H, dd, *J* 7.5, 10 Hz), 7.03 (1H, d, *J* 3 Hz), 7.11 (1H, dt, *J* 5, 7.5 Hz), 7.20 (1H, t, *J* 8 Hz).
36a	7-OMe (*S*)	mp 87-88 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.5 Hz), 1.30 (9H, s), 3.95 (3H, s), 4.03 (1H, sept, *J* 7 Hz), 4.36 (1H, m), 4.50 (1H, m), 6.44 (1H, d, *J* 3 Hz), 6.63 (1H, d, *J* 7.5 Hz), 6.97 (1H, m), 6.98 (1H, t, *J* 7.5 Hz), 7.20 (1H, dd, *J* 1, 8 Hz).
37a	7-Et (*S*)	mp 115-116 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 3 Hz), 1.33 (3H, t, *J* 7.5 Hz), 1.39 (9H, s), 3.06 (2H, m), 3.98 (1H, sept, *J* 7 Hz), 4.18 (1H, dd, *J* 7, 14 Hz), 4.36 (1H, m), 6.49 (1H, d, *J* 3 Hz), 6.99 (1H, dd, *J* 1, 7.5 Hz), 7.01 (1H, d, *J* 7 Hz), 7.04 (1H, d, *J* 7 Hz), 7.46 (1H, dd, *J* 1, 7.5 Hz).
38a	4-Cl (*S*)	mp 90-91 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 4.08 (2H, m), 4.26 (1H, m), 6.61 (1H, dd, *J* 1, 3 Hz), 7.09 (1H, d, *J* 4 Hz), 7.10 (1H, m), 7.11 (1H, d, *J* 4 Hz), 7.35 (1H, m).
39a	6-SMe (*S*)	NMR δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.6 Hz), 1.41 (9H, br s), 2.53 (3H, s), 4.04-4.49 (4H, br m), 6.44 (1H, d, *J* 3.0 Hz), 7.00 (1H, d, *J* 2.9 Hz), 7.09 (1H, d, *J* 8.3 Hz), 7.41 (1H, s), 7.51 (1H, d, *J* 8.3 Hz); IR (Nujol)ν_{max}/cm^{-1} 3362, 2924, 1681, 1533, 1174, 1061 and 803; Found C, 63.26, H,

		7.58, N, 8.59%. $C_{17}H_{24}N_2O_2S$ requires C, 63.72, H, 7.55, N, 8.74%.
40a	6-SEt (*S*)	mp 112-113 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.7 Hz), 1.27 (3H, t, *J* 7.3 Hz), 1.41 (9H, br s), 2.93 (2H, q, *J* 7.2 Hz), 4.02-4.49 (4H, m), 6.45 (1H, d, *J* 3.0 Hz), 7.03 (1H, d, *J* 3.0 Hz), 7.14 (1H, d, *J* 7.0 Hz), 7.47 (1H, s) and 7.51 (1H, d, *J* 8.4 Hz); IR (film)ν_{max}/cm^{-1} 3370, 2924, 1684, 1524, 1466, 1162, 1057 and 790; Found C, 64.49, H, 8.00, N, 8.15%. $C_{18}H_{26}N_2O_2S$ requires C, 64.64, H, 7.83, N, 8.37%.
41a	6-SPr (*S*)	mp 74-75 °C; NMR δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.1 Hz), 1.10 (3H, d, *J* 6.9 Hz), 1.41 (9H, br s), 1.59-1.68 (2H, m), 2.89 (2H, t, *J* 6.8 Hz), 4.02-4.40 (4H, br m), 6.44 (1H, d, *J* 3.0 Hz), 7.02 (1H, d, *J* 3.0 Hz), 7.13 (1H, d, *J* 8.0 Hz), 7.47 (1H, s) and 7.50 (1H, d, *J* 8.7 Hz); IR (Nujol)ν_{max}/cm^{-1} 3357, 2927, 1686, 1534, 1460, 1377, 1175, 1062 and 810.
42a	6-S^{i}Pr (*S*)	mp 74-75 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.6 Hz), 1.27 (6H, d, *J* 6.9 Hz), 1.42 (9H, br s), 3.30-3.34 (1H, m), 4.04-4.50 (4H, br m), 6.48 (1H, d, *J* 3.5 Hz), 7.07 (1H, d, *J* 3.1 Hz), 7.19 (1H, d, *J* 9.6 Hz) and 7.53 (2H, m); IR (Nujol)ν_{max}/cm^{-1} 3374, 2926, 1690, 1515, 1463, 1174, 1080 and 813.

Table 8: Indolines prepared using General Method B, step (b)

No		**Data**
10b	6-Cl (*S*)	NMR δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 8 Hz), 1.46 (9H, s), 2.97 (1H, t, *J* 8 Hz), 3.04-3.10 (1H, m), 3.45-3.56 (1H, m), 3.88-3.98 (1H, m), 4.52 (1H, brs), 6.42 (1H, brs), 6.58-

		6.62 (1H, m) and 6.95-7.01 (1H, m).
11b	7-OBn (*RS*)	IR ν_{max} (Nujol)/cm^{-1} 3368, 1683, 1536, 1461, 1369, 1249, 1170, 1059 and 743; NMR δ_H (400 MHz, $CDCl_3$), 0.96 (3H, d, *J* 6.5 Hz), 1.36 (9H, br s), 2.89-3.13 (3H, m), 3.21-3.35 (1H, m), 3.45-3.87 (3H, m), 5.04 (2H, s), 6.63 (1H, t, *J* 8 Hz), 6.75 (2H, d, *J* 8 Hz) and 7.3-7.45 (5H, m).
12b	6-Br (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1679, 1604, 1503, 1360, 1169, 1014 and 775; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 2.88-3.06 (1H, m), 3.41-3.53 (2H, m), 3.85-3.93 (2H, m), 4.47 (1H, brs), 6.52-6.54 (1H, m), 6.70-6.74 (1H, m) and 6.87-6.89 (1H, m).
13b	6-OMe (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1687, 1622, 1529, 1460, 1285, 1173, 1059 and 812; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6 Hz), 1.50 (9H, s), 2.85-2.95 (2H, m), 2.9-3.1 (2H, m), 3.33-3.52 (2H, m), 3.80 (3H, s), 3.85-3.95 (1H, m), 4.45-4.49 (1H, brs), 6.1 (1H, brs), 6.16-6.18 (1H, m) and 6.93-6.95 (1H, m).
14b	5-Me, 6-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1684, 1533, 1462, 1291, 1058 and 816; NMR δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 7.5 Hz), 1.42 (9H, s), 2.42 (3H, s), 2.86-2.91 (1H, m), 2.96-3.0 (1H, m), 3.33-3.44 (4H , m), 3.86-3.91 (1H, m), 4.46 (1H, brs), 6.41 (1H, s) and 6.87 (1H, s).
15b	5-F, 6-Cl (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1678, 1541, 1457, 1058 and 733; NMR δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.5 Hz), 1.39 (9H, s), 2.90-3.01 (4H, m), 3.40-3.50 (3H, m), 3.84-3.91 (1H, m), 4.43 (1H, brs), 6.33 (1H, d, *J* 6 Hz) and 6.79 (1H, d, *J* 6 Hz)
16b	5F, 6-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1677, 1540, 1501, 1170, 1058 and 732; NMR δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.5 Hz), 1.39 (9H, s), 2.90-3.01 (4H, m), 3.40-3.50 (3H, m), 3.84-

		3.91 (1H, m), 4.43 (1H, brs), 6.33 (1H, d, *J* 6 Hz) and 6.79 (1H, d, *J* 6 Hz)
17b	5-F, 7-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1684, 1532, 1249, 1173, 1057, 839 and 643; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5 Hz), 1.39 (9H, s), 2.96-3.05 (2H, m), 3.26-3.34 (1H, m), 3.48 (1H, dd, *J* 14, 8 Hz), 3.57-3.66 (1H, m), 3.92-3.99 (1H, m), 4.61 (1H, brs) and 6.77-6.69 (2H, m).
18b	6-Br (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1679, 1604, 1537, 1503, 1361, 1169, 1014 and 775; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6 Hz), 1.42 (9H, s), 2.88-3.07 (4H, m), 3.38-3.54 (2H, m), 3.84-3.94 (1H, m), 4.47 (1H, brs), 6.52-6.54 (1H, m), 6.70-6.75 (1H, m) and 6.85-6.89 (1H, m).
19b	7-Br (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1689, 1603, 1526, 1366, 1175, 1051 and 748; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.5 Hz), 1.38 (9H, s), 3.0 (2H, t, *J* 8.5 Hz), 3.14-3.39 (1H, m), 3.43-3.51 (1H, m), 3.58-3.67 (1H, m), 3.74-3.81 (1H, m), 3.96-4.04 (1H, m), 4.69 (1H, brs), 6.52 (1H, t, *J* 7.5 Hz), 6.97 (1H, d, *J* 7.5 Hz) and 7.17 (1H, d, *J* 7.5 Hz).
20b	7-Br (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1531, 1465, 1251, 1173, 1056 and 745; NMR δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 7 Hz), 1.35 (9H, s), 3.28-3.37 (1H, m), 3.40-3.48 (1H, m), 3.54-3.64 (2H, m), 3.92-4.0 (2H, m), 4.67 (1H, brs), 6.49 (1H, t, *J* 8 Hz), 6.93-6.96 (1H, m) and 7.14 (1H, dd, *J* 8.5, 1 Hz).
21b	6,7-dichloro (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1684, 1533, 1462, 1250, 1059 and 778; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6 Hz), 1.35 (9H, s), 2.94-3.01 (2H, m), 3.50-3.86 (5H, m), 4.59 (1H, brs), 6.74-6.77 (1H, m) and 6.81-6.84 (1H, m).
22b	5,6-difluoro (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1679, 1536, 1505, 1254, 1056 and 748; NMR δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5 Hz), 1.46 (9H, s), 2.90-3.07 (4H, m), 3.39-3.55 (2H, m), 3.80-3.89 (1H, m), 4.50 (1H, brs), 6.27 (1H, dd, *J* 10.5, 6 Hz) and

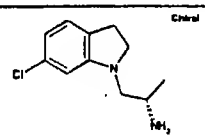
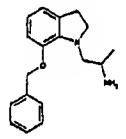
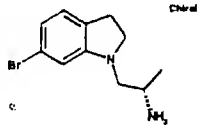
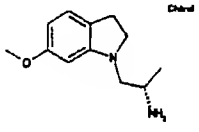
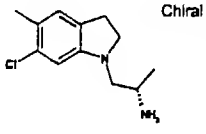
		6.85-6.90 (1H, m).
23b	6,7-dichloro (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1601, 1534, 1463, 1250, 1060 and 778; NMR δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.5 Hz), 1.36 (9H, s), 2.94-3.00 (2H, m), 3.49-3.56 (2H, m), 3.97-4.03 (3H, m), 4.58 (1H, brs), 6.74 (1H, d, *J* 7.5 Hz) and 6.82 (1H, d, *J* 7.5 Hz).
24b	6-CF_3 (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1679, 1540, 1463, 1159, 1115, 799 and 659; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6 Hz), 1.41 (9H, s), 3.0-3.11 (4H, m), 3.44-3.59 (2H, m), 3.92-3.98 (1H, m), 4.48 (1H, brs), 6.59 (1H, brs), 6.87 (1H, d, *J* 9 Hz) 7.10 (1H, d, *J* 6.5 Hz).
25b	5-F, 6-Br (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1667, 1539, 1500, 1267, 1169, 1057 and 730; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 7 Hz), 1.44 (9H, s), 2.92 (1H, m), 3.0 (1H, dd, *J* 8.5, 5.5 Hz), 3.84-3.92 (2H, m), 4.48 (1H, brs), 6.51 (1H, d, *J* 4.5 Hz) and 6.83 (1H, d, *J* 8Hz).
26b	6-CF_3 (*R*)	IR ν_{max} (Nujol)/cm^{-1} 1679, 1618, 1540, 1159, 1016, 799 and 659; NMR δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6 Hz), 1.38 (9H, s), 3.0 (1H, t, *J* 8 Hz), 3.08 (2H, d, *J* 7 Hz), 3.43-3.57 (2H, m), 3.88-3.96 (1H, m), 4.44 (1H, brs), 7.53 (1H, brs), 6.86 (1H, d, *J* 7 Hz) and 7.07 (1H, d, *J* 7 Hz).
27b	6-Cl, 7-F (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1681, 1557, 1400, 1313, 1263, 1206, 926 and 678; NMR δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 7 Hz) 1.38 (9H, s) 2.59-3.02 (2H, m) 3.21 (1H, dd, *J* 14, 5 Hz) 3.39-3.49 (2H, m) 3.61-3.69 (2H, m) 4.45-4.53 (1H, brs) 6.55-6.60 (1H, m) 6.68-6.71 (1H, m)
28b	5-Cl (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1683, 1529, 1490, 1461, 1245, 1168 and 807; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 7 Hz), 1.44 (9H, s), 2.93-3.09 (4H, m), 3.38-3.51 (2H, m), 3.84-3.92 (1H, m), 4.49 (1H, brs), 6.36 (1H, d, *J* 7 Hz) and 6.97-

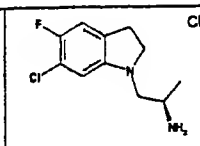
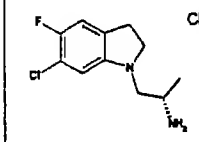
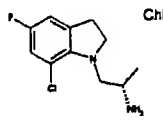
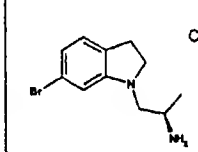
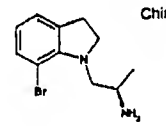
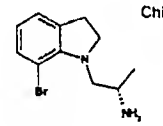
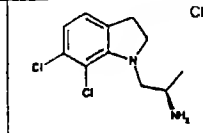
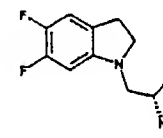
		7.01 (2H, m).
29b	5-F (*S*)	IR ν_{max} (Nujol)/cm^{-1} 1687, 1538, 1464, 1235, 1169, 867 and 796; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.5 Hz), 1.47 (9H, s), 2.95-3.08 (1H, m), 3.40 (1H, dd, *J* 16, 8.5 Hz), 3.47 (1H, dd, J 16, 8.5 Hz), 3.87-3.95 (1H, m), 4.57 (1H, brs), 6.39 (1H, dd, *J* 8, 3.5 Hz), 6.76 (1H, td, *J* 8.5, 2 Hz) and 6.81-6.85 (1H, m).
30b	5-F, 6-MeS (*S*)	mp 96-100 °C; IR ν_{max} (Nujol)/cm^{-1} 3364, 2924, 2854, 1678, 1611, 1528, 1500, 1455, and 1163; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.0 Hz), 1.44 (9H, s), 2.44 (3H, s), 2.88-2.99 (3H, m), 3.05 (1H, dd, *J* 13.5, 5.5 Hz), 3.37 (1H, q, *J* 8.5 Hz), 3.46 (1H, q, *J* 8.5 Hz), 3.83-3.95 (1H, m), 4.42-4.62 (1H, brm), 6.42 (1H, d, *J* 6.0 Hz), 6.77-6.81 (1H, m).
31b	5-F, 6-EtS (*S*)	IR ν_{max} (film)/cm^{-1} 3363, 2970, 2927, 1688, 1495, 1366, 1248, 1169, and 1057; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.5 Hz), 1.27 (3H, t, *J* 7.0 Hz), 1.44 (9H, s), 2.84-3.07 (6H, m), 3.38 (1H, q, *J* 8.5 Hz), 3.46 (1H, q, *J* 8.5 Hz), 3.82-3.95 (1H, m), 4.41-4.61 (1H, brm), 6.46 (1H, d, *J* 6.5 Hz), 6.80 (1H, d, *J* 9.0 Hz).
32b	4-Me (*S*)	mp 75-76 °C; Found: C, 69.91; H, 9.01; N, 9.56%. $C_{17}H_{26}N_2O_3$ requires C, 70.31; H, 9.02; N, 9.64%; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.5 Hz), 1.44 (9H, s), 2.20 (3H, s), 2.92 (2H, t, *J* 8.5 Hz), 3.03 (1H, dd, *J* 6, 13.5 Hz), 3.08 (1H, dd, *J* 6, 14 Hz), 3.42 (1H, q, *J*, 8.5 Hz), 3.48 (1H, q, *J* 8.5 Hz), 3.90 (1H, sept, *J* 6.5 Hz), 6.35 (1H, d, *J* 7.5 Hz), 6.52 (1H, d, *J* 7.5 Hz), 6.98 (1H, t, *J* 7.5 Hz).
33b	5-Br (*S*)	Found: C, 54.06; H, 6.53; N, 7.66%. $C_{16}H_{23}N_2BrO_2$ requires C, 54.09; H, 6.53; N, 7.88%; NMR δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5 Hz), 1.42 (9H, s), 2.97 (2H, t, *J*

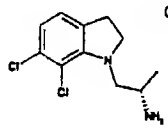
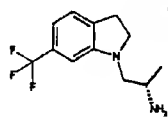
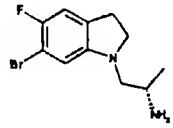
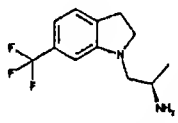
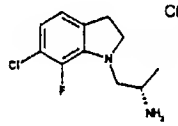
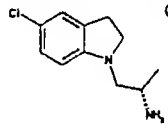
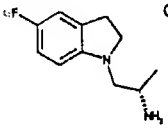
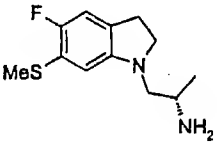
		8.5 Hz), 2.98 (1H, m), 3.08 (1H, dd, *J* 6, 14 Hz), 3.42 (1H, q, *J*, 8.5 Hz), 3.45 (1H, sept, *J* 8.5 Hz), 3.88 (1H, m), 6.35 (1H, d, *J* 8.5 Hz), 7.11 (1H, m), 7.14 (1H, m).
34b	5,6-di-OMe (*S*)	IR ν_{max} (film-DCM)/cm^{-1} 3359, 2974, 2933, 2835, 1694, 1617, 1054, 1455, 1366, 1235, 1206, 1169, 1088, 1059, 1022, 843 and 748; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.5 Hz), 2.95 (3H, m), 3.06 (1H, m), 3.41 (2H, m), 3.81 (3H, s), 3.86 (3H, s), 3.87 (1H, m), 6.30 (1H, brs.), 6.75 (1H, s).
35b	4-F (*S*)	IR ν_{max} (Nujol)/cm^{-1} 3345, 2925, 2854, 1602, 1632, 1534, 1469, 1364, 1253, 1226, 1169, 1057, 1024 and 748; NMR δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 3.03 (2H, t, *J* 8.5 Hz), 3.10 (2H, dt, *J* 6, 14 Hz), 3.50 (2H, sept, *J* 8.5 Hz), 3.90 (1H, m), 6.26 (1H, d, *J* 8 Hz), 6.36 (1H, t, *J* 8.5 Hz), 7.00 (1H, dt, *J* 5.5, 8.5 Hz).
36b	7-OMe (*S*)	mp 108-109 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.5 Hz), 1.39 (9H, s), 3.01 (2H, m), 3.20 (1H, dd, *J* 5, 13 Hz), 3.39 (1H, q, *J* 8.5 Hz), 3.59 (2H, m), 3.82 (3H, s), 3.88 (1H, m), 6.68 to 6.78 (3H, m).
37b	7-Et (*S*)	mp 81-82 °C; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.5 Hz), 1.28 (3H, d, *J* 6.5 Hz), 1.44 (9H, s), 2.67 (2H, q, *J* 7.5 Hz), 3.05 (3H, m), 3.19 (1H, dd, *J* 7.5, 13.5 Hz), 3.48 (2H, m), 3.90 (1H, m), 6.81 (1H, m), 6.95 (1H, d, *J* 7.5 Hz), 6.99 (1H, d, *J* 7.5 Hz).
38b	4-Cl (*S*)	NMR δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 3.05 (2H, t, *J* 8.5 Hz), 3.11 (2H, m), 3.50 (1H, q, *J* 8.5 Hz), 3.58 (1H, m), 3.91 (1H, m), 6.39 (1H, m), 6.65 (1H, m), 7.00 (1H, t, *J* 7.5 Hz); HPLC (Column: Supelcosil ABZ$^+$ [170 mm x 4.6 mm], particle size 5 μM; Eluent: methanol, 10 mM aqueous ammonium acetate solution (7:3); Flow Rate 1.0 mL/min; Detection Wavelength λ = 210 nM) Retention Time: 4.55 min.

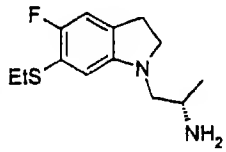
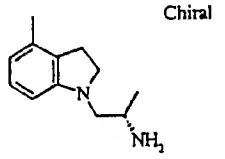
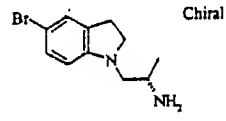
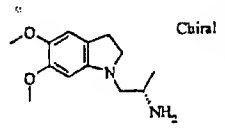
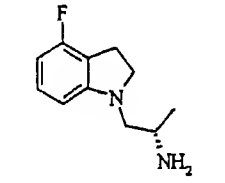
39b to 42b		intermediates used immediately

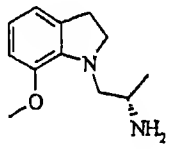
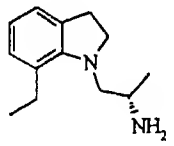
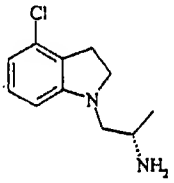
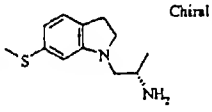
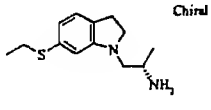
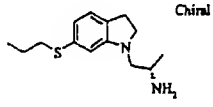
Table 9: **Examples 10-42.** Indolines prepared using General Method B, step (c)

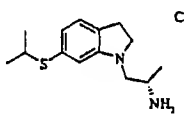
No	Structure	Data
10		Fumarate. mp 164 °C (dec.); Found C, 56.35; H, 6.12; N, 9.30%. $C_{11}H_{15}ClN_2.0.75\ C_4H_4O_4$ requires: C, 56.47; H, 6.09; N, 9.41%.
11		Trifluoroacetate. mp 201-203 °C; Found: C, 60.57; H, 5.86; N, 6.99%. $C_{18}H_{22}N_2O.CF_3CO_2H$ requires: C, 60.60; H, 5.85; N, 7.06%; IR ν_{max} (Nujol)/cm^{-1} 1676, 1464, 1204, 1135, 1057, 841, 754 and 724; NMR δ_H (400 MHz, DMSO-d_6), 0.93, (3H, d, *J* 6.5 Hz), 2.82-2.98 (2H, m), 3.09-3.18 (1H, m), 3.23-3.5 (4H, m), 5.07 (2H, s), 6.63 (1H, t, *J* 8 Hz), 6.72 (1H, d, *J* 7.5 Hz), 6.82 (1H, d, *J* 7 Hz), 7.29-7.49 (5H, m) and 7.76-8.01 (3H, br s).
12		Fumarate. mp 191-192 °C; Found: C, 49.51; H, 5.48; N, 8.59%. $C_{11}H_{15}BrN_2.0.6\ C_4H_4O_4$ requires: C, 49.55; H, 5.40; N, 8.62%.
13		Fumarate. mp 175-6 °C; IR ν_{max} (Nujol/cm^{-1}) 1623, 1568, 1525, 1497, 1462, 1379, 1343, 1276, 1196, 1176, 1097 and 666; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, d, *J* 7.5Hz), 2.78-2.87 (2H, m), 2.87-2.96 (2H, m), 3.07-3.17 (2H, m), 3.22-3.31 (1H, m), 3.39-3.49 (1H, m) 3.70 (3H, s), 6.1-6.15 (1H, m), 6.17-6.21 (1H, m) and 6.83-6.93 (1H, m).
14		Fumarate. mp 172-174 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.52 (3H, d, *J* 6.5 Hz), 2.49 (3H, s), 3.28 (1H, dd, *J* 13, 5.5 Hz) 3.5-3.85 (6H, m), 6.93 (1H, s) and 7.31 (1H, s).

15		Fumarate. mp 198-200 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, d, J 7 Hz) 2.82-3.01 (2H, m) 3.18-3.38 (3H, m) 3.46-3.54 (1H, m) 6.69 (1H, d, J 7 Hz) 7.08 (1H, d, J 7 Hz)
16		NMR δ_H (400 MHz, DMSO-d_6) 1.12 (3H, d, J 7.5 Hz), 2.91-2.98 (2H, m), 3.07 (1H, dd, J 7.5 Hz), 3.26-3.34 (1H, m), 3.33-3.40 (1H, m), 3.50-3.59 (2H, m), 6.65 (1H, d, J 7 Hz) and 7.09 (1H, d, J 7 Hz).
17		Fumarate. mp 195-196 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.12 (3H, d, J 6.5 Hz), 2.93-2.99 (1H, m), 3.15-3.51 (6H, m) and 6.91-6.98 (2H, m).
18		Fumarate. mp 193-194 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.13 (3H, d, J 6.5 Hz), 2.82-2.90 (1H, m), 2.94 (1H, dd, J 13.5, 5 Hz), 3.10-3.18 (1H, dd, J 13.5, 8 Hz), 3.21-3.37 (2H, m), 3.45-3.53 (2H, m), 6.65-6.69 (2H, m) and 6.93 (1H, d, J 7.5 Hz).
19		Fumarate. mp 197 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, d, J 6.5 Hz), 2.93-3.0 (2H, m), 3.30-3.57 (5H m), 6.56 (1H, dd, J 8, 7 Hz), 7.05 (1H, dd, J 7, 1 Hz) and 7.15 (1H, dd, J 8, 1 Hz).
20		Fumarate. mp 202-204 °C; NMR δ_H (400 MHz, DMSO d_6) 1.13 (3H, d, J 6.5 Hz), 2.93-3.56 (7H, m), 6.54 (1H, t, J 7.5 Hz), 7.02-7.05 (1H, m) and 7.15 (1H, dd, J 7.5, 1 Hz).
21		Fumarate. mp 213-214 °C ; NMR δ_H (400 MHz, DMSO-d_6) 1.11 (3H, d, J 6 Hz), 2.91-2.97 (1H, m), 3.22-3.63 (6H, m), 6.82 (1H, d, J 8 Hz) and 6.98 (1H, d, J 8 Hz).
22		Fumarate. mp 165 °C (dec.); NMR δ_H (400 MHz, DMSO-d_6) 1.21 (3H, d, J 6.5 Hz), 2.84-2.93 (2H, m), 2.99 (1H, dd, J 13, 5 Hz), 3.22 (1H, dd, J 13, 8 Hz), 3.28-3.41 (2H, m), 3.48-3.56 (1H, m), 6.64 (1H, dd, J, 12, 6.5 Hz) and 7.08-7.13 (1H, m).

23		Fumarate. mp 176-178 °C ; NMR δ_H (400 MHz, DMSO-d_6) 1.16 (3H, d, J 6.5 Hz), 2.94-3.00 (1H, m), 3.29-3.63 (6H, m), 6.85 (1H, d, J 8 Hz) and 7.01 (1H, d, J 8 Hz).
24		Fumarate. mp 197-199 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, d, J 6 Hz), 2.99-3.06 (2H, m), 3.35-3.62 (5H, m), 6.79 (1H, brs), 6.89 (1H, d, J 7.5 Hz) and 7.20 (1H, d, J 7.5 Hz).
25		Fumarate. mp 195-196 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.18 (3H, d, J 6.5 Hz), 2.86-2.92 (2H, m), 2.96 (1H, dd, J 14, 5 Hz), 3.15-3.23 (2H, m), 3.37-3.26 (1H, m), 3.47-3.54 (1H, m), 6.78 (1H, d, J 6 Hz) and 7.07 (1H, d, J 8.5 Hz).
26		Fumarate. mp 196-197 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.14 (3H, d, J 6 Hz), 2.95-3.01 (1H, m), 3.14-3.58 (6H, m), 6.75 (1H, brs), 6.85 (1H, d, J 8 Hz) and 7.17 (1H, d, J 8 Hz).
27		Fumarate. NMR δ_H (400 MHz, DMSO-d_6) 1.14 (3H, d, J 6 Hz), 2.98-3.03 (1H, m), 3.19-3.56 (6H, m), 6.73 (1H, dd, J 6.5, 6 Hz) and 6.90 (1H, d, J 8 Hz).
28		Fumarate. mp 207-210 °C ; NMR δ_H (400 MHz, DMSO-d_6) 1.13 (3H, d, J 6.5 Hz), 2.89-2.98 (2H, m), 3.05-3.51 (5H, m), 6.52 (1H, d, J 8 Hz) and 7.05-7.07 (2H, m).
29		Fumarate. mp 175-176 °C ; NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, J 6.5 Hz), 2.87-2.99 (2H, m), 3.33-3.41 (2H, m), 3.43-3.51 (3H, m), 6.54 (1H, dd, J 8.5, 4.5 Hz), 6.82 (1H, td, J 8.5, 2.5 Hz) and 6.94 (1H, dd, J 8.5, 2.5 Hz).
30		Fumarate. mp 96-100 °C; IR ν_{max} (Nujol)/cm^{-1} 3364, 2924, 2854, 1678, 1611, 1528, 1500, 1455, and 1163; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, J 7.0 Hz), 1.44 (9H, s), 2.44 (3H, s), 2.88-2.99 (3H, m), 3.05 (1H, dd, J 13.5, 5.5 Hz), 3.37 (1H, q, J 8.5 Hz), 3.46 (1H, q, J 8.5 Hz), 3.83-3.95 (1H, m), 4.42-4.62 (1H, brm), 6.42 (1H, d, J 6.0 Hz), 6.77-6.81 (1H, m).

31		Fumarate. mp 164-168 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1702, 1626, 1458, 1378, 1227, 1041, 791 and 652; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, t, *J* 7.0 Hz), 1.22 (3H, d, *J* 6.5 Hz), 2.81-3.01 (5H, m), 3.19-3.31 (2H, m), 3.32-3.41 (1H, m), 3.45-3.54 (1H, m), 6.44 (2H, s), 6.59 (1H, d, *J* 6.5 Hz), 6.95 (1H, d, *J* 9.5 Hz), 8.00-10.31 (3H, brm).
32		Fumarate. mp 161-162 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6.5 Hz), 2.14 (3H, s), 2.85 (2H, m), 2.99 (1H, dd, *J* 5.5, 13.5 Hz), 3.22 (1H, dd, *J* 5.5, 13.5 Hz), 3.30 (1H, t, *J* 8.5 Hz), 3.36 (1H, m), 3.47 (1H, dt, *J* 6.5, 8.5 Hz), 6.40 (1H, d, *J* 8 Hz), 6.45 (2H, s), 6.46 (1H, d, *J* 8 Hz), 6.92 (1H, t, *J* 8 Hz); Found: C, 59.37; H, 7.32; N, 8.55%. $C_{16}H_{22}N_2O_4.H_2O$ requires C, 59.24; H, 7.46; N, 8.64%.
33		Fumarate. NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6.5 Hz), 2.94 (2H, m), 3.02 (1H, dd, *J* 5.5, 14 Hz), 3.23 (1H, dd, *J* 5.5, 13.5 Hz), 3.31 (1H, t, *J* 8.5 Hz), 3.38 (1H, m), 3.50 (1H, dt, *J* 7, 8.5 Hz), 6.46 (2H, s), 6.53 (1H, d, *J* 8.5 Hz), 7.14 (1H, dd, *J* 2.5, 8.5 Hz), 7.19 (1H, d, *J* 2.5 Hz); Found: C, 48.51; H, 5.16; N, 7.46%. $C_{15}H_{19}BrN_2O_4$ requires C, 48.53; H, 5.16; N, 7.54%.
34		Fumarate. mp 166-167 °C (dec.); NMR δ_H (400 MHz, DMSO-d_6) 1.26 (3H, d, *J* 6.5 Hz), 2.84 (2H, m), 2.93 (1H, dd, *J* 5, 13.5 Hz), 3.29 (1H, dd, *J* 5, 13.5 Hz), 3.38 (1H, m), 3.45 (1H, dt, *J* 8.5, 5.5 Hz), 3.65 (3H, s), 3.73 (3H, s), 6.42 (1H, s), 6.46 (2H, s), 6.78 (1H, s); Found: C, 56.52; H, 6.91; N, 7.63%. $C_{17}H_{24}N_2O_6.0.5H_2O$ requires C, 56.50; H, 6.97; N, 7.75%.
35		Fumarate. mp 167-168 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6.5 Hz), 2.96 (2H, m), 3.06 (1H, dd, *J* 5.5, 13.5 Hz), 3.28 (1H, dd, *J* 7.5, 13.5 Hz), 3.40 (2H, m), 3.56 (1H, m), 6.40 (1H, t, *J* 8.5 Hz), 6.38-6.43 (2H, m), 6.46 (2H, s), 7.03 (1H, dt, *J* 6,8 Hz); Found: C, 58.03; H, 6.18; N,

		9.01%. $C_{15}H_{19}N_2FO_4$ requires C, 58.06; H, 6.17; N, 9.02%.
36		Fumarate. mp 155-156 °C (dec.); NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, J 6 Hz), 2.92 (2H, t, J 9 Hz), 3.36 (5H, m), 3.75 (3H, s), 6.45 (2H, s), 6.66 (1H, t, J 7.5 Hz), 6.73 (1H, dd, J 1, 7.5 Hz), 6.76 (1H, d, J 7.5 Hz).
37		Fumarate. mp 182-183 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.17 (3H, t, *J* 7.5 Hz), 1.28 (3H, d, *J* 6.5 Hz), 2.63 (2H, m), 2.93 (2H, m), 3.10 (1H, dd, *J* 7, 13 Hz), 3.21 (1H, dd, *J* 5.5, 13 Hz), 3.35 (2H, m), 6.45 (2H, s), 6.72 (1H, t, *J* 7.5 Hz), 6.89 (1H, d, *J* 7.5 Hz), 6.95 (1H, dd, *J* 1, 7.5 Hz).
38		Hemi-fumarate. mp 190-192 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.14 (3H, d, *J* 6.5 Hz), 2.96 (2H, m), 3.13 (1H, dd, *J* 8, 14 Hz), 3.25 (1H, m), 3.41 (1H, q, *J* 8.5 Hz), 3.54 (2H, dd, *J* 7, 8.5 Hz), 6.41 (1H, s), 6.48 (1H, d, *J* 8 Hz), 6.58 (1H, d, *J* 8 Hz), 7.01 (1H, t, *J* 8 Hz).
39		Fumarate. mp. darkens 165 °C, melts 167-168 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.22 (3H, d, *J* 6.4 Hz), 2.42 (3H, s), 2.86-2.89 (2H, m), 2.97-3.02 (1H, dd, *J* 13.8, 5.3 Hz), 3.25-3.49 (4H, m), 6.43 (2H, s), 6.48-6.50 (2H, m) and 6.96; IR (Nujol)ν_{max}/cm^{-1} 2920, 1706, 1464, 979 and 652.
40		Fumarate. mp. darkens 140 °C, melts 146-147 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.17-1.23 (6H, m), 2.83-2.94 (4H, m), 2.97-3.02 (1H, dd, *J* 14.0, 5.6 Hz), 3.22-3.53 (4H, m), 6.45 (2H, s), 6.56 (2H, m) and 6.97 (1H, d, *J* 7.4 Hz); IR (Nujol)ν_{max}/cm^{-1} 2924, 1676, 1463, 1377, 1278 and 650.
41		Fumarate. mp. 147-148 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.94 (3H, t, *J* 7.0 Hz), 1.22 (3H, d, *J* 6.0 Hz), 1.50-1.57 (2H, m), 2.83-2.91 (4H, m), 3.00 (1H, dd, *J* 13.5, 5.1 Hz), 3.23-3.51 (4H, m), 6.44 (2H, s), 6.54-6.56 (2H, m), 6.95 (1H, d, *J* 8.1 Hz); IR (Nujol)ν_{max}/cm^{-1} 2925, 1706, 1604, 1464, 957

		and 652.
42		Fumarate. mp. 164-165 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.18-1.23 (9H, m), 2.86-3.03 (3H, m), 3.26-3.51 (5H, m), 6.44 (2H, s), 6.49-6.61 (2H, m), 6.98 (1H, d, *J* 7.5 Hz); IR (Nujol)ν_{max}/cm^{-1} 2924, 1725, 1598, 1461, 1312, 880, 790 and 636.

Indole Syntheses:

6-Chloro-5-fluoro-1*H*-indole

2-Fluoro-4-methyl-5-nitroaniline

Concentrated nitric acid (20 g) was added dropwise over 90 min to a stirred solution of 2-fluoro-4-methylaniline (25 g, 200 mmol) in concentrated sulfuric acid (250 mL) at –10 °C. The mixture was poured onto ice (1 L) and the solution adjusted to pH 13 using solid sodium hydroxide (CARE: EXOTHERMIC REACTION) keeping the internal temperature below 80 °C. The mixture was extracted with ether (3 x) and the combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to leave the product (32 g, 94%) as an orange solid. A recrystallised sample (heptane, ethyl acetate) gave mp 80-82 °C; $C_7H_7FN_2O_2$ requires: C, 49.42; H, 4.15; N, 16.46%. Found C, 49.60; H, 4.15; N, 16.57%.

3-Chloro-4-fluoro-6-methylnitrobenzene

A solution of sodium nitrite (7.6 g, 110 mmol) in water (20 mL) was added dropwise over 30 min at 0 °C to a stirred suspension of 2-fluoro-4-methyl-5-nitroaniline (17g, 100 mmol) in concentrated hydrochloric acid (200 mL). The mixture was stirred at 0 °C for 20 min then transferred to a dropping funnel and added dropwise over 30 min to a stirred suspension of copper(I)chloride (16 g) in concentrated hydrochloric acid (150 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h

then poured onto ice-water (1.5 L) and extracted with ethyl acetate (3 x). The combined organic extracts were washed with brine, dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane] to give the product (14.2 g, 75%) as a yellow solid. An analytical sample was recrystallised (heptane) to give a white solid: mp 57-58 °C ; NMR δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* 7.2 Hz), 7.13 (1H, d, *J* 9.1 Hz), 2.6 (3H, s).

6-Chloro-5-fluoro-1*H*-indole

N,N-Dimethylformamide dimethylacetal (6.3 ml, 45 mmol) was added in one portion to a stirred solution of 3-chloro-4-fluoro-6-methylnitrobenzene (7.0 g, 37 mmol) in *N,N*-dimethylformamide (30 mL) at 130 °C under Ar. The mixture was stirred at 130 °C for 2 h, cooled to room temperature, concentrated *in vacuo* and partitioned between ethyl acetate and water and the aqueous was extracted with ethyl acetate (2 x). The combined organic extracts were washed with brine, dried (magnesium sulfate), concentrated *in vacuo*, dissolved in methanol/tetrahydrofuran (1:1; 100 mL) and Raney Nickel®, 50% wt. in water, (5 g) was added. The mixture was cooled to 0 °C and hydrazine hydrate (3 mL, 59 mmol) was added dropwise over 2 min. The mixture was warmed to room temperature, stirred for 1 h then cooled to 0 °C and hydrazine hydrate (1.5 mL) was added over 2 min. The mixture was warmed to room temperature, stirred for 1 h and filtered through celite®. The filter-cake was washed with tetrahydrofuran and the filtrate was concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-dichloromethane (4:1)] to give the product (3.2 g, 51%) as an off-white solid. An analytical sample was recrystallised (heptane) to give a white solid: mp 105-107 °C; NMR δ_H (400 MHz, $CDCl_3$) 8.01 (1H, br. s), 7.40 (1H, d, J 6 Hz), 7.35 (1H, d, J 9.4 Hz), 7.25 (1H, t, J 2.8 Hz), 6.50-6.51 (1H, m).

7-Chloro-5-fluoroindole

N-(2-Chloro-4-fluorophenyl)-2-(hydroxyimino)-acetamide

A solution of chloral hydrate (6.25 g, 37.8 mmol), sodium sulfate decahydrate (48.3 g, 340 mmol) and water (100 mL) was added to a stirred solution of 2-chloro-4-

fluoroaniline (5.0 g, 34 mmol), hydroxylamine hydrochloride (9.19 g, 130 mmol), water (50 mL) and concentrated hydrochloric acid (3 mL). The reaction mixture was heated under reflux for 1 h, cooled to room temperature, stirred for 16 h and filtered. The filter-cake was recrystallised (methanol-water) to give the product (5.58 g, 75% yield) as a pale brown solid: IR ν_{max} (Nujol)/cm^{-1} 1655, 1613, 1536, 1267, 1191, 1021, 853 and 558; NMR δ_H (400 MHz, DMSO-d_6) 7.20-7.29 (1H, m), 7.51-7.57 (1H, m), 7.78-7.84 (1H, m), 9.61 (1H, s) and 12.36 (1H, s).

7-Chloro-5-fluoroindole-2,3-dione

N-(2-Chloro-4-fluorophenyl)-2-(hydroxyimino)-acetamide (5.4 g, 24.9 mmol) was added portionwise to conc. sulfuric acid (70 mL) at 70 °C. The mixture was stirred for 1 h, poured onto ice-water (200 mL) and filtered. The filter-cake was dried *in vacuo* to give crude 7-chloro-5-fluoroindole-2,3-dione which was used immediately without further purification.

7-Chloro-5-fluoroindole

To a stirred solution of lithium aluminium hydride (0.57 g, 15 mmol) in THF (20 mL) at 0 °C under Ar was added portionwise 7-chloro-5-fluoroindole-2,3-dione. The mixture was heated under reflux for 4 h, cooled to 0 °C and water (0.5 mL) was added. The mixture was stirred for 5 min then treated with aqueous sodium hydroxide solution (2 N, 0.5 mL) followed by water (0.5 mL) and filtered through a pad of celite®. The filter-cake was washed with tetrahydrofuran and the filtrate was concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (3:1)] to give the product (0.31 g, 37% yield) as a blue oil: IR ν_{max} (film)/cm^{-1} 3459, 1575, 1485, 1341, 1120 and 722; NMR δ_H (400 MHz, $CDCl_3$) 6.55 (1H, t, *J* 2.5 Hz) 7.01 (1H, dd, *J* 9,2 Hz) 7.21 (1H, m) 7.29 (1H, t, *J* 2.5 Hz) 8.33 (1H, brs).

6-Chloro-7-fluoroindole

Methyl 2-azido-3-(4-chloro-3-fluorophenyl)propenoate

Sodium (2.32 g, 100 mmol) was added portionwise to stirred methanol (200 mL) at 0 °C under Ar. The mixture was stirred for 1 h and cooled to –15 °C. A solution of 4-chloro-3-fluorobenzaldehyde (4.0 g, 25 mmol), methyl azidoacetate (8.7 g, 75 mmol) in methanol (20 mL) was added. The mixture was stirred for 3 h, warmed to 4 °C and stirred for 16 h and partitioned between water (300 mL) and ether (3 x 200 mL). The organic extracts were combined and washed with brine (2 x), dried (magnesium sulfate) and concentrated *in vacuo* to give an orange solid. Recrystallisation (methanol) gave the product (5.09 g, 80% yield) as a pale yellow solid: IR ν_{max} (Nujol)/cm^{-1} 2115, 1708, 1616, 1234, 1060, 896, 818 and 616; NMR δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s) 6.64 (1H, s) 7.35-7.46 (2H, m) 7.74-7.78 (1H, m).

Methyl 6-chloro-7-fluoroindole-2-carboxylate

A solution of methyl 2-azido-3-(4-chloro-3-fluorophenyl)propenoate (15.08 g, 59 mmol) in xylene (200 mL) was added dropwise to stirred xylene (1 L) under reflux. The mixture was stirred for 3 h, cooled to room temperature, concentrated *in vacuo* and purified by column chromatography [SiO_2; isopropyl ether-hexane (5:2)] to give the product (2.3 g, 17% yield) as a colourless solid: IR ν_{max} (Nujol)/cm^{-1} 3298, 1709, 1460, 1377, 1204 and 737; NMR δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s) 7.09-7.15 (1H, m) 7.21 (1H, m) 7.38 (1H, m) and 9.05 (1H, brs).

6-Chloro-7-fluoroindole-2-carboxylic acid

A stirred solution of methyl 6-chloro-7-fluoroindole-2-carboxylate (2.3 g, 10 mmol), tetrahydrofuran (20 mL) and aqueous sodium hydroxide solution (2 N, 20 mL) was heated under reflux for 16 h. The mixture was cooled to room temperature and partitioned between aqueous sulfuric acid (2 M, 30 mL) and ethyl acetate (3 x 30 mL). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to give the product (2.1 g, 98% yield) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 1681, 1557, 1263, 1206, 926 and 840; NMR δ_H (400 MHz, DMSO-d_6) 7.01-7.12 (2H, m) and 7.31-7.34 (1H, m).

6-Chloro-7-fluoroindole

A solution of 6-chloro-7-fluoroindole-2-carboxylic acid (2.1 g, 9.8 mmol) and diphenyl ether (30 mL) was heated under reflux for 4 h, cooled to room temperature and purified by column chromatography [SiO_2; heptane-ethyl acetate (99:1 to 10:1)] to give the product (1.04 g, 63% yield) as a pale brown oil: IR ν_{max} (Nujol)/cm^{-1} 3460, 1573, 1490, 1446, 1201, 802 and 619; NMR δ_H (400 MHz, $CDCl_3$) 6.44 (1H, brs) 7.04-7.09 (1H, m) 7.21-7.26 (1H, m) 7.30-7.34 (1H, m) and 8.40 (1H, brs).

6-Bromo-5-fluoroindole

3-Bromo-4-fluoro-6-methylnitrobenzene

A solution of sodium nitrite (7.6 g, 110 mmol) in water (30 mL) was added dropwise over 15 min to a stirred suspension of 2-fluoro-4-methyl-5-nitroaniline (17 g, 100 mmol) in hydrobromic acid, (48%, 150 mL) and water (30 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min then added portionwise over 10 min to a stirred suspension of copper(I)bromide (16.5 g, 112 mmol) in hydrobromic acid (48%, 50 mL) and water (90 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min then warmed to room temperature and stirred for 3 h. The mixture was poured onto ice-water (500 mL) and extracted with ethyl acetate (3 x). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (19:1)] to give the product (11.8 g, 50%) as an off-white solid: IRν_{max} (nujol)/cm^{-1} 2925, 2855, 1571, 1523, 1478, 1349, 1264, 1103, 895, 671 and 589; NMR δ_H (400 MHz, $CDCl_3$) 8.27 (1H, d, *J* 6.5), 7.10 (1H, d, *J* 9.1), 2.60 (3H, s).

6-Bromo-5-fluoroindole

N,N-Dimethylformamide dimethylacetal (8.5 mL, 60 mmol) was added in one portion to a stirred solution of 3-bromo-4-fluoro-6-methylnitrobenzene (11.8 g, 50 mmol) in *N,N*-dimethylformamide (30 mL) at room temperature under Ar. The mixture was heated to 120 °C, stirred for 16 h then concentrated *in vacuo* to leave a crude oil. The oil

was crystallised [methanol-dichloromethane (4:1)] to give a purple solid (4.5 g). The solid was dissolved in methanol/tetrahydrofuran (1:1; 30 mL) and Raney Nickel® (1 g) was added. The mixture was cooled to 0 °C and hydrazine hydrate (0.8 mL, 16 mmol) was added in one portion. The mixture was stirred at 0 °C for 90 min then a further aliquot of hydrazine hydrate (0.8 mL) was added. The mixture was stirred at 0 °C for 30 min then filtered through celite® and the filter cake was washed with tetrahydrofuran. The filtrate was concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-dichloromethane (4:1)] to give the *product* (1.7 g, 16%) as an off-white solid: IR ν_{max} (nujol)/cm^{-1} 3395, 2925, 2855, 1570, 1469, 1451, 1408, 1314, 1145, 1105, 865, 763 and 502; NMR δ_H (400 MHz, $CDCl_3$) 7.85 (1H, br. s), 7.55 (1H, d, *J* 5.5 Hz), 7.34 (1H, d, *J* 9 Hz), 7.23 (1H, t, J 2.8 Hz), 6.49-6.51 (1H, m).

5-Fluoro-6-methylthioindole

5-Fluoro-6-methylthioindole-2,3-dione

Sodium thiomethoxide (5.93 g, 84.6 mmol) was added to a solution of 5,6-difluoroindole-2,3-dione (7.75 g, 42.3 mmol) in dimethylformamide (400 mL). The reaction was stirred at room temperature for 1 h, then poured onto ice (2 L). The resulting solid was collected by filtration, washed with water and dried at 40 °C under vacuum to give a brown solid (3.12 g, 35%): mp 296 °C; $C_9H_6F_1NO_2S$ requires: C, 51.18; H, 2.86; N, 6.63; S, 15.18%. Found C, 50.95; H, 2.85; N, 6.58; S, 15.35%; IR ν_{max} (Nujol)/cm^{-1} 3285, 2925, 2854, 1760, 1714, 1611, 1465 and 1036; NMR δ_H (400 MHz, DMSO-d_6) 2.58 (3H, s), 6.71 (1H, d, *J* 6.0 Hz), 7.38 (1H, d, *J* 9.0 Hz), 11.02 (1H, brs).

5-Fluoro-6-methylthioindole

5-Fluoro-6-methylthioindole was prepared from 5-fluoro-6-methylthioindole-2,3-dione according to the method described in the preparation of 7-chloro-5-fluoroindole as a white solid (1.21 g, 37%): mp 51 °C; C_9H_8FNS requires: C, 59.65; H, 4.45; N, 7.73; S, 17.69%. Found C, 59.75; H, 4.44; N, 7.72; S, 17.65%; IR ν_{max} (Nujol)/cm^{-1} 3461, 3408, 3361, 2925, 2855, 1455, 1304 and 1137; NMR δ_H (400 MHz, $CDCl_3$) 2.49 (3H,

s), 6.49-6.51 (1H, m), 7.22 (1H, t, *J* 3.0 Hz), 7.30 (1H, d, *J* 10.0 Hz), 7.36 (1H, d, *J* 6.5 Hz), 8.0-8.25 (1H, brm).

6-Ethylthio-5-fluoroindole

6-Ethylthio-5-fluoroindole-2,3-dione

6-Ethylthio-5-fluoroindole-2,3-dione was prepared from 5,6-difluoroindole-2,3-dione using sodium thioethoxide according to the method described in the synthesis of 5-fluoro-6-methylthioindole as a brown solid (2.53 g, 19%): mp 215 °C; IR ν_{max} (Nujol)/cm^{-1} 3286, 2926, 2855, 1766, 1712, 1619, 1467 and 1038; NMR δ_H (400 MHz, DMSO-d_6) 1.32 (3H, t, *J* 7.5 Hz), 3.13 (2H, q, *J* 7.5 Hz), 6.77 (1H, d, *J* 6.0 Hz), 7.39 (1H, d, *J* 8.5 Hz), 10.97 (1H, brs).

6-Ethylthio-5-fluoroindole

6-Ethylthio-5-fluoroindole was prepared from 6-ethylthio-5-fluoroindole-2,3-dione according to the method described in the synthesis of 7-chloro-5-fluoroindole as a pale green oil (0.49 g, 23%): IR ν_{max} (film)/cm^{-1} 3426, 2969, 2927, 1565, 1471, 1454, 1307, 1140 and 1101; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.5), 2.91 (2H, q, *J* 7.5 Hz), 6.48-6.51 (1H, m), 7.23 (1H, t, *J* 2.5 Hz), 7.31 (1H, d, *J* 10.0 Hz), 7.46 (1H, d, *J* 6.0 Hz), 8.01-8.25 (1H, brm).

6-Methylthioindole

To a stirred suspension of potassium hydride (30% dispersion in mineral oil, 0.68 g, 5.10 mmol) in dry tetrahydrofuran (20 mL) at 0 °C, under Ar, was added a solution of 6-bromoindole (1.0 g, 5.1 mmol) in tetrahydrofuran (10 mL). After 15 mins, the solution was cooled to –78 °C and *tert*-butyllithium (1.7 M, 6.0 mL, 10 mmol) was added dropwise. The mixture was stirred for a further 15 mins and then dimethyl disulphide (0.92 mL, 10.2 mmol) was added dropwise. The solution was warmed gradually to room temperature, then diluted carefully with saturated ammonium chloride solution (20 mL). The mixture was extracted with ether (2 x 50 mL). The combined organic

extracts were dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-dichloromethane (1:1)] to give the product as a pale-yellow solid (0.56 g, 68%): mp. 91-92 °C; NMR δ_H (400 MHz, $CDCl_3$) 2.51 (3H, s), 6.49 (1H, m), 7.09-7.16 (2H, m), 7.35 (1H, s), 7.54 (1H, d, *J* 8.2 Hz) and 8.09 (1H, br s); IR (Nujol)ν_{max}/cm^{-1} 3388, 2925, 1459, 1311, 1098, 810, 717 and 527.

6-Ethylthioindole

6-Ethylthioindole was prepared according to the method described for the synthesis of 6-methylthioindole as a clear oil (0.73 g, 81%). NMR δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.6 Hz), 2.93 (2H, q, *J* 7.5 Hz), 6.51 (1H, m), 7.16-7.18 (2H, m), 7.45 (1H, s), 7.55 (1H, d, *J* 8.3 Hz) and 8.10 (1H, br s); IR (film)ν_{max}/cm^{-1} 3404, 2970, 1616, 1450, 1310, 810 and 723.

6-n-Propylthioindole

6-n-Propylthioindole was prepared according to the method described for the synthesis of 6-methylthioindole as a clear oil, which solidified on standing (0.88 g, 91%). mp. 54-55 °C; NMR δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.4 Hz), 1.56-1.65 (2H, m), 2.87 (2H, dd, *J* 14.5, 7.1 Hz), 6.51 (1H, m), 7.16-7.18 (2H, m), 7.45 (1H, s), 7.54 (1H, d, *J* 8.0 Hz), and 8.10 (1H, br s); IR (Nujol)ν_{max}/cm^{-1} 3388, 2924, 1614, 1452, 1311, 810, 718 and 524.

6-Isopropylthioindole

6-Isopropylthioindole was prepared according to the method described for the synthesis of 6-methylthioindole as a clear, viscous oil (0.59 g, 61%). NMR δ_H (400 MHz, $CDCl_3$) 1.26 (6H, d, *J* 7.0 Hz), 3.25-3.32 (1H, m), 6.52 (1H, m), 7.19-7.56 (2H, m) and 8.12 (1H, br s); IR (Nujol)ν_{max}/cm^{-1} 3416, 2960, 1613, 1449, 1338, 1050, 810 and 606.

General Method C:

Example 43: (*S*)-1-(6-Phenylindolin-1-yl)-2-propylamine fumarate

Step a: (*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-phenylindoline (43a)

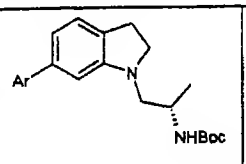
To a stirred solution of palladium(II)acetate (0.011 g, 0.05 mmol) and triphenylphosphine (0.052 g, 0.2 mmol) in tetrahydrofuran (5 mL) under Ar was added (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-bromoindoline (0.34 g, 1 mmol). The mixture was stirred for 10 min and treated with a solution of phenyl boronic acid (0.24 g, 2 mmol) in ethanol (2 mL) followed by aqueous sodium bicarbonate solution (2 M, 5 mL). The mixture was heated under reflux for 2 h and cooled to room temperature. The mixture was partitioned between ether (50 mL) and water (2 x 20 mL). The organic layer was dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (6:1)] to give the product (0.24 g, 69% yield) as a colourless oil. Data for (43a) are included in Table 10 with the compounds prepared using General Method C, step (a).

Step (b): (*S*)-1-(6-Phenylindolin-1-yl)-2-propylamine fumarate (43)

(*S*)-1-(6-Phenylindolin-1-yl)-2-propylamine fumarate was prepared according to the method described in General Method B, step (c) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-phenylindoline to give the product (0.12 g, 65% yield) as a white solid. Data for (43) are included in Table 11 with the compounds prepared using General Method C, step (b).

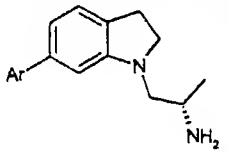
The compounds shown in Tables 10 and 11 were prepared according to General Method C using the appropriate aryl boronic acid.

Table 10: Indolines prepared using General Method C, step (a)

No		Data
43a	Ph	IR ν_{max} (Nujol)/cm^{-1} 1682, 1529, 1456, 1367, 1170, 1064 and 756; NMR δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6 Hz), 1.41 (9H, s), 3.06 (1H, t, *J* 8.5 Hz), 3.14 (1H, d, *J* 6.5 Hz), 3.46-3.56 (2H, m), 3.94 (1H, m), 4.56 (1H, brs), 6.68 (1H, brs), 6.88 (1H, dd, *J* 8, 1.5 Hz), 7.13 (1H, d, *J* 7.5 Hz), 7.29-7.34 (1H, m), 7.38-7.43 (1H, m) and 7.54-7.58 (1H, m).
44a	4-Cl-C_6H_4	IR ν_{max} (Nujol)/cm^{-1} 1691, 1459, 1377, 1171, 1055, 832 and 801; NMR δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.5 Hz) 1.45 (9H, s) 4.02-4.49 (7H, m) 6.51 (1H, d, *J* 3 Hz) 7.06-7.12 (2H, m) 7.42 (1H, brs) 7.54 (1H, d, *J* 9 Hz).
45a	4-F-C_6H_4	IR ν_{max} (Nujol)/cm^{-1} 1679, 1530, 1168, 1064, 838 and 805; NMR δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, J 6 Hz), 1.41 (9H, s), 3.0-3.15 (3H, m), 3.95 (1H, brs), 6.63 (1H, brs), 6.81-6.85 (1H, m), 7.05-7.13 (3H, m), and 7.50-7.53 (2H, m).
46a	4-OMe-C_6H_4	IR ν_{max} (Nujol)/cm^{-1} 1694, 1609, 1518, 1365, 1245, 1177, 833 and 804; NMR δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6 Hz), 1.41 (9H, s), 2.98-3.03 (1H, m), 3.1-3.13 (1H, m), 3.42-3.53 (2H, m), 3.84 (3H, s), 4.58 (1H, brs), 6.63 (1H, brs), 6.82-6.85 (1H, m), 6.94 (2H, d, *J* 8.5 Hz), 7.09 (1H, d *J* 7 Hz) and 7.49 (2H, d, *J* 8.5 Hz).
47a	3-pyridinyl	IR ν_{max} (Nujol)/cm^{-1} 1690, 1526, 1458, 1176, 1053 and 788; NMR δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5 Hz), 1.43 (9H, s), 3.07 (1H, t, *J* 8.5 Hz), 3.14-3.20 (2H, m), 3.49-3.62 (2H, m), 3.95-4.01 (1H, m), 4.57 (1H, brs), 6.66 (1H, brs), 7.84 (1H, d, *J* 7 Hz), 7.18 (1H, d, *J* 7 Hz), 7.35-7.39 (1H, m), 7.90 (1H, dt, *J* 7.5, 1.5 Hz), 8.59-8.64 (1H, m) and 8.85 (1H, brs).

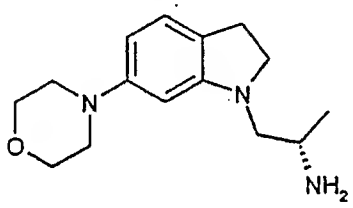
48a	3-thiophenyl	IR ν_{max} (Nujol)/cm^{-1} 1686, 1514, 1357, 1172, 1080 and 775; NMR δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6 Hz), 1.45 (9H, s), 3.03 (2H, t, *J* 8.5 Hz), 3.12-3.16 (2H, m), 3.44-3.50 (2H, m), 3.93-4.0 (1H, m), 4.59 (1H, brs), 6.73 (1H, brs), 6.29 (1H, dd, *J* 7, 1.5 Hz) 7.11 (1H, d, *J* 7 Hz), 7.36-7.38 (2H, m) and 7.41-7.43 (1H, m).

Table 11: **Examples 43-48.** Indolines prepared using General Method C, step (b)

No		**Data**
43	Ph	Fumarate. mp 153-154 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6 Hz), 2.90-2.98 (2H, m), 3.06 (1H, dd, *J* 13, 5 Hz), 3.23-3.45 (2H, m), 3.50-3.56 (2H, m), 6.84 (1H, d, *J* 1.5 Hz), 6.87 (1H, dd, *J* 7.5, 1.5 Hz), 7.11 (1H, d, *J* 7.5 Hz), 7.28-7.33 (2H, m), 7.38-7.43 (1H, m) and 7.58-7.62 (1H, m).
44	4-Cl-C_6H_4	Fumarate. mp 171-173 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.26 (3H, d, J 6.5 Hz), 2.93-2.99 (2H, m), 3.07-3.13 (2H, m), 3.29-3.49 (2H, m), 3.521-3.60 (1H, m), 6.88-6.91 (2H, m), 7.13 (1H, d, J 7 Hz), 7.48 (2H, d, J 9 Hz) and 7.67 (2H, d, J 9 Hz).
45	4-F-C_6H_4	Fumarate. mp 148-149 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6 Hz), 3.05 (1H, dd, *J* 13, 5 Hz), 3.27-3.56 (6H, m), 6.80-6.86 (2H, m), 7.09 (1H, d, *J* 6.5 Hz), 7.23 (2H, t, *J* 8 Hz) and 7.60-7.66 (2H, m).
46	4-OMe-C_6H_4	Fumarate. mp 174-176 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, d, *J* 6.5 Hz), 2.87-2.95 (2H, m), 3.18-3.57 (5H, m), 3.79 (3H, s), 6.78 (1H, brs), 6.82 (1H, dd, *J* 7, 1 Hz), 6.99 (2H, d, *J* 8.5 Hz), 7.08 (1H, d, *J* 8 Hz) and 7.55 (2H, d, *J* 8.5 Hz).

47	3-pyridinyl	Fumarate. mp 155 °C (dec.); NMR δ_H (400 MHz, DMSO-d_6) 1.27 (3H, d, *J* 6 Hz), 2.93-3.02 (2H, m), 3.12 (1H, dd, *J* 13, 4.5 Hz), 3.32-3.60 (4H, m), 6.93-6.96 (1H, m), 7.17 (1H, d, *J* 8 Hz), 7.43-7.47 (1H, m), 8.01-8.06 (1H, m), 8.52-8.55 (1H, m) and 8.86-8.88 (1H, brs).
48	3-thiophenyl	Fumarate. mp 182-186 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.27 (3H, d, *J* 6 Hz), 2.91-2.99 (2H, m), 3.09 (1H, dd, *J* 13, 5.5 Hz), 3.28-3.58 (5H, m), 6.94-6.98 (1H, m), 7.08 (1H, d, *J* 8 Hz), 7.59 (1H, dd, *J* 5, 3 Hz), 7.53 (1H, dd, *J* 5, 1.5 Hz) and 7.78-7.80 (1H, m).

Example 49: (*S*)-1-[6-(4-Morpholinyl)indolin-1-yl]-2-propylamine fumarate



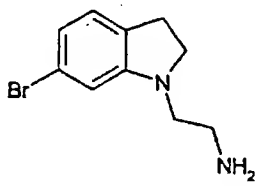
(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-(4-morpholinyl)indoline

A mixture of palladium(II)acetate (0.004 g, 0.016 mmol), BINAP (0.01 g, 0.016 mmol), cesium carbonate (0.15 g, 0.45 mmol), toluene (2 mL), (*S*)-1-[2-(tert-butoxycarbonylamino)propyl-6-bromoindoline (0.11 g, 0.32 mmol) and morpholine (0.04 mL, 0.38 mmol) under argon was heated at 100 °C for 16 h, concentrated *in vacuo* and purified by column chromatography [SiO_2; isopropyl ether-heptane (1:1)] to give the product (0.05 g, 45% yield) as a pale yellow oil: IR ν_{max} (Nujol)/cm^{-1} 1678, 1615, 1522, 1459, 810 and 767; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6 Hz), 1.47 (9H, s), 2.94 (1H, t, *J* 7 Hz), 3.06 (1H, dd, *J* 10, 5 Hz), 3.11-3.18 (4H, m), 3.37-3.55 (2H, m), 3.82-3.95 (5H, m), 4.60 (1H, brs), 6.17-6.26 (2H, m) and 6.99 (1H, d, *J* 7.5 Hz).

(*S*)-1-[6-(4-Morpholinyl)indolin-1-yl]-2-propylamine fumarate

(*S*)-1-[6-(4-Morpholinyl)indolin-1-yl]-2-propylamine fumarate was prepared according to the method in Example 10 using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-(4-morpholinyl)indoline to give the product (0.02 g, 43%) as a beige solid: mp 188-191 °C (dec); IR ν_{max} (Nujol)/cm^{-1} 1744, 1649, 1576, 1457, 1309, 1175, 984, 784 and 643.

Example 50: 2-(6-Bromoindolin-1-yl)-1-ethylamine fumarate



2-(6-Bromoindol-1-yl)-1-ethylamine fumarate

To a stirred mixture of powdered sodium hydroxide (0.41 g, 10.2 mmol), tetrabutylammonium hydrogensulfate (0.034 g, 0.1 mmol), 6-bromoindole (0.5 g, 2.5 mmol) and acetonitrile (15 mL) was added 2-chloroethylamine hydrochloride (0.31 g, 2.75 mmol). The mixture heated under reflux for 16 h and partitioned between water (30 mL) and ether (2 x 30 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; ethyl acetate-methanol-0.880 ammonia solution (90:9:1)] to give a pale brown oil. The oil was dissolved in 2-propanol (10 mL) and the solution was heated to reflux, fumaric acid (0.29 g, 2.5 mmol) was added and the mixture was cooled to room temperature and filtered. The filter-cake was dried *in vacuo* to give the product (0.72 g, 81% yield) as a white solid: mp 214-216 °C; NMR δ_H (400 MHz, DMSO-d_6) 3.08 (2H, t, *J* 8 Hz), 4.33 (2H, t, *J* 8 Hz), 6.47-6.52 (1H, m), 7.14-7.19 (1H, m), 7.41-7.44 (1H, m), 7.52 (1H, d, *J* 6.5 Hz) and 7.82 (1H, brs).

1-[2-(tert-Butoxycarbonylamino)ethyl]-6-bromoindole

To a stirred mixture of 2-(6-bromoindole-1-yl)-1-ethylamine fumarate (1.4 mmol), tert-butanol (3 mL), water (3 mL) and powdered sodium hydroxide (0.22 g, 5.5 mmol) was addded di-tert-butyl-dicarbonate (0.3 g, 1.4 mmol). The mixture was stirred for 16 h

and partitioned between water (20 mL) and ethyl acetate (2 x 30 mL). The organic extracts were combined, washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (5:1)] to give the product (0.25 g, 53% yield) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 1683, 1528, 1459, 1303, 1164, 1060 and 717; NMR δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s), 3.45-3.51 (2H, m), 4.25-4.30 (2H, m), 4.53 (1H, brs), 6.73 (1H, d, *J* 3 Hz), 7.05 (1H, d, *J* 3 Hz), 7.20 (1H, dd, *J* 7.5, 2 Hz) and 7.50 (1H, d, *J* 7.5 Hz).

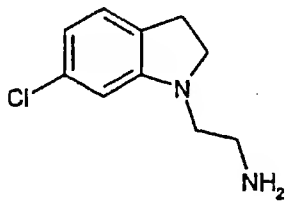
1-[2-(tert-Butoxycarbonylamino)ethyl]-6-bromoindoline

1-[2-(tert-Butoxycarbonylamino)ethyl]-6-bromoindoline was prepared according to General Method B, step (b) using 1-[2-(tert-butoxycarbonylamino)ethyl]-6-bromoindole to give the product 0.19 g (93% yield) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 1684, 1603, 1532, 1302, 984 and 781; NMR δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s) 2.92 (2H, t, *J* 8 Hz) 3.17 (2H, t, *J* 6 Hz) 3.31-3.36 (1H, m) 3.4 (2H, t, *J* 8 hz) 4.78 (1H, brs), 6.57 (1H, brs) 6.75 (1H, dd, *J* 7.5, 2 Hz) and 6.90-6.95 (1H, m).

2-(6-Bromoindolin-1-yl)-1-ethylamine fumarate

2-(6-Bromoindolin-1-yl)-1-ethylamine fumarate was prepared according to General Method B, step (c) using 1-[2-(tert-butoxycarbonylamino)ethyl]-6-bromoindole to give the product 0.14 g (73% yield) as a white solid: mp 203-206 °C; NMR δ_H (400 MHz, DMSO-d_6) 2.80-2.90 (2H, m) 3.14-3.17 (2H, m) 3.35-3.41 (4H, m) 6.64-6.69 (2H, m) and 6.93 (1H, d, *J* 8 Hz).

Example 51: 2-(6-Chloroindolin-1-yl)-1-ethylamine fumarate



2-(6-Chloroindol-1-yl)-1-ethylamine fumarate

2-(6-Chloroindol-1-yl)-1-ethylamine fumarate was prepared according to the method described in Example 50 using 6-chloroindole to give the product (1.34 g, 64% yield) as a colourless solid: mp. 210-213 °C; NMR δ_H (400 MHz, $CDCl_3$) 3.01 (2H, t, *J* 6.5 Hz), 4.26 (2H, t, *J* 6.5 Hz), 6.46-6.48 (2H, m), 7.02 (1H, dd, *J* 8, 1.5), 7.41 (1H, d, *J* 3 Hz) 7.54 (1H, d, *J* 8 Hz) and 7.65-7.66 (1H, m).

1-[2-(tert-Butoxycarbonylamino]ethyl)-6-chloroindole

1-[2-(tert-Butoxycarbonylamino]ethyl)-6-chloroindole was prepared according to the method described in Example 50 using 2-(6-chloroindol-1-yl)-1-ethylamine fumarate to give the product (1.02 g, 86% yield) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 1686, 1611, 1538, 1467, 1279, 1143, 796 and 718; NMR δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s), 3.45-3.51 (2H, m), 4.21-4.27 (2H, m), 4.54 (1H, brs), 6.49 (1H, brs), 7.05-7.09 (2H, m), 7.34 (1H, s) and 7.53 (1H, d, *J* 8.5 Hz).

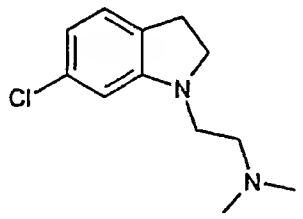
1-[2-(tert-Butoxycarbonylamino]ethyl)-6-chloroindoline

1-[2-(tert-Butoxycarbonylamino]ethyl)-6-chloroindoline was prepared according to General method B, step (b) using 1-[2-(tert-butoxycarbonylamino]ethyl)-6-chloroindole to give the product 0.75 g (75 % yield) as a colourless solid: IR ν_{max} (Nujol)/cm^{-1} 1684, 1606, 1533, 1362, 1165 and 782; NMR δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 2.92 (2H, t, *J* 8 Hz), 3.15 (2H, t, *J* 6 Hz), 3.28-3.35 (1H, m), 3.40 (2H, t, *J* 8 Hz), 4.76 (1H, brs), 6.38-6.40 (1H, s), 6.56-6.59 (1H, m) and 6.90-6.93 (1H, m).

2-(6-Chloroindolin-1-yl)-1-ethylamine fumarate

2-(6-Chloroindolin-1-yl)-1-ethylamine fumarate was prepared according to General Method B, step (c) using 1-[2-(tert-butoxycarbonylamino]ethyl)-6-chloroindoline to give the product 0.39 g (55% yield) as a white solid: mp 195-196 °C; NMR δ_H (400 MHz, DMSO d_6) 2.88 (2H, t, *J* 8.5 Hz), 2.98 (2H, t, *J* 6 Hz), 3.28 (2H, t, *J* 6 Hz), 3.41 (2H, t, *J* 8.5 Hz), 6.55-6.59 (2H, m) and 6.99 (1H, d, *J* 7.5 Hz).

Example 52: N,N-Dimethyl-2-(6-Chloroindolin-1-yl)-1-ethylamine fumarate



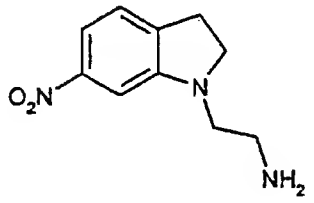
N,N-Dimethyl-2-(6-chloroindol-1-yl)-1-ethylamine fumarate

N,N-Dimethyl-2-(6-chloroindol-1-yl)-1-ethylamine fumarate was prepared according to the method described in Example 50 using 6-chloroindole and 1-chloro-2-(dimethylamino)ethane to give the product (0.5 g, 22% yield) as a white solid: mp 163-165 °C; NMR δ_H (400 MHz, $CDCl_3$) 2.93 (6H, s), 3.37 (2H, t, *J* 6.5 Hz), 4.95 (2H, t, *J* 6.5 Hz), 7.13 (1H, d, J 3 Hz), 7.68-7.72 (1H, m), 8.11 (1H, d, *J* 3 Hz), 8.22 (1H, d, *J* 8 Hz) and 8.29-8.31 (1H, m).

N,N-Dimethyl-2-(6-chloroindolin-1-yl)-1-ethylamine fumarate

N,N-Dimethyl-2-(6-chloroindolin-1-yl)-1-ethylamine fumarate was prepared according to General Method B, step (b) using *N,N*-dimethy-2-(6-chloroindol-1-yl)-1-ethylamine fumarate to give the product 0.19 g (27% yield) as a colourless solid: mp 144-146 °C; NMR δ_H (400 MHz, DMSO-d_6) 2.41 (6H, s), 2.72 (2H, t, *J* 7 Hz), 2.88 (2H, t, *J* 8 Hz), 3.27 (2H, t, *J* 7 Hz), 3.43 (2H, t, *J* 8 Hz), 6.55 (1H, dd, *J* 7.5, 2.5 Hz), 6.58 (1H, brs) and 6.99 (1H, d, *J* 7.5 Hz).

Example 53: 2-(6-Nitroindolin-1-yl)-1-ethylamine fumarate



1-(6-Nitroindolin-1-yl)-acetonitrile

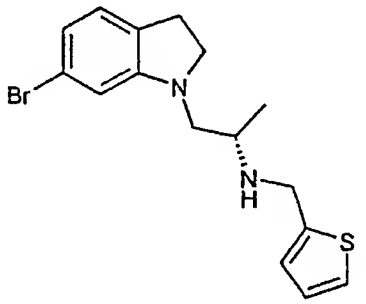
A stirred mixture of 6-nitroindoline (2.0 g, 12 mmol), potassium carbonate (3.36 g, 24 mmol), sodium iodide (3.65 g, 24.4 mmol), acetone (20 mL) and chloroacetonitrile (1.5 mL, 24 mmol) was heated under reflux for 16 h. The mixture was cooled to room temperature, filtered and the filter-cake washed with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (9:1)] to give the product (1.3 g, 53% yield) as a pale yellow solid: IR ν_{max} (Nujol)/cm^{-1} 1615, 1513, 1487, 1343, 1293, 1145, 804 and 739; NMR δ_H (400 MHz, $CDCl_3$) 3.11 (2H, t, *J* 7.5 Hz), 3.59 (2H, t, *J* 7.5 Hz), 4.14 (2H, s), 7.19-7.23 (1H, m), 7.31-7.33 (1H, m) and 7.69-7.72 (1H, m).

2-(6-Nitroindolin-1-yl)-1-ethylamine fumarate

Borane-dimethylsulfide complex (0.25 mL, 2.6 mmol) was added dropwise to a stirred solution of 1-(6-nitroindolin-1-yl)-acetonitrile (0.38 g, 1.9 mmol) in tetrahydrofuran (10 mL) under Ar. The mixture was heated under reflux for 4 h then cooled to room temperature and stirred for 16 h. The mixture was cooled to 0 °C, hydrochloric acid (3 M, 10 mL) was added and the mixture was heated under reflux for 1 h. The mixture was cooled to room temperature and washed with ethyl acetate (2 x 10 mL). The aqueous layer was partitioned between aqueous sodium hydroxide solution (2 M, 20 mL) and dichloromethane (3 x 30 mL). The combined dichloromethane extracts were dried (magnesium sulfate) and concentrated *in vacuo* to give a pale yellow oil. The oil was dissolved in 2-propanol (3 mL) and the solution was heated to reflux then fumaric acid (0.1 g, 0.87 mmol) was added. The mixture was cooled to room temperature and

filtered. The filter-cake was dried *in vacuo* to give the product (0.36 g, 59% yield) as a white solid: mp 197 °C (dec.); NMR δ_H (400 MHz, DMSO-d_6) 2.99 (2H, t, *J* 7 Hz), 3.09 (2H, t, *J* 7 Hz), 3.38 (2H, t, *J* 7.5 Hz), 3.54 (2H, t, *J* 8.5 Hz), 6.44 (2H, s), 7.23-7.27 (2H, m) and 7.48 (1H, dd, *J* 8, 2 Hz).

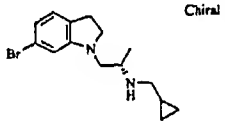
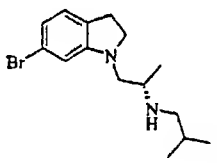
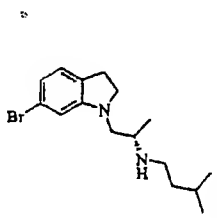
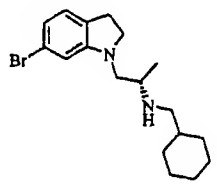
Example 54: (*S*) *N*-(2-thiophenyl)methyl-1-(6-bromoindolin-1-yl)-2-propylamine hydrochloride

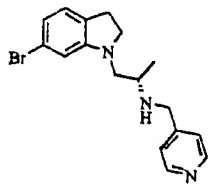


A mixture of (*S*)-(6-bromoindolin-1-yl)-2-propylamine (0.039 g, 0.15 mmol), thiophene-2-carboxaldehyde (0.034 g, 0.30 mmol) and methanol (1 mL) was shaken for 3 h. To the mixture was added Amberlite IRA-400 borohydride resin (2.5 mmol/g – BH_4, 0.12 g, 0.3 mmol) and the mixture was shaken for 18 h. To the mixture was added PS-benzaldehyde (2.5 mmol/g –CHO, 0.12 g, 0.3 mmol) and the mixture was shaken for 18 h and filtered. The filter-cake was washed with dichloromethane (2 x 1 mL) and methanol (2 x 1 mL) and the filtrate was concentrated *in vacuo*. The concentrate was dissolved in dichloromethane (2 mL) and Amberlyst-15 (0.5 g) was added. The mixture was shaken for 1 h and filtered. The filter-cake was washed with dichloromethane (2 x 1 mL) and methanol (2 x 1 mL), suspended in methanolic ammonia solution (2 M, 1 mL, 2 mmol), shaken for 1 h, and filtered. The filter-cake was washed (dichloromethane) and the filtrate was concentrated *in vacuo*. The residue was treated with ethereal hydrogen chloride solution (1 M, 1 mL, 1 mmol) and concentrated *in vacuo* to give the product as a beige solid (0.037 g, 63%): mp 151-154 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.37 (3H, d, *J* 6.5 Hz) 2.92 (2H, m) 3.15 (1H, dd, *J* 6,14 Hz) 3.31 (1H, q, *J* 9 Hz) 3.46 (2H, m) 3.55 (1H, m) 4.47 (2H, m) 6.79 (1H, d, *J* 7.5 Hz) 6.80 (1H, s) 6.99 (1H, d, *J* 8 Hz) 7.13 (1H, m) 7.41 (1H, d, *J* 2.5 Hz) 7.66 (1H, d, *J* 5 Hz).

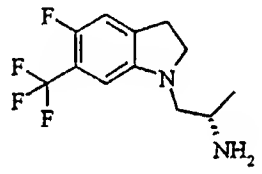
The compounds shown in Table 12 were prepared from (*S*)-(6-bromoindolin-1-yl)-2-propylamine and the appropriate aldehyde according to the method described in Example 54.

Table 12: **Examples 55-59.** Indolines prepared according to the method described in Example 54.

No	Structure	Data
55		HCl. mp 155-156 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.38 (2H, dd, *J* 2, 4.5 Hz), 0.57 (2H, t, *J* 7.5 Hz), 1.12 (1H, m), 1.28 (3H, d, *J* 6.5 Hz), 2.81 (1H, m), 2.90 (2H, t, *J* 8 Hz), 2.92 (1H, m), 3.16 (1H, m), 3.35 (1H, q, *J* 8.5 Hz), 3.50 (3H, m), 6.73 (1H, dd, *J* 1.5, 7.5 Hz), 6.80 (1H, d, *J* 1.5 Hz), 6.97 (1H, d, *J* 7.5 Hz).
56		HCl. mp 151-153 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.98 (6H, dd, *J* 1, 6.5 Hz), 1.32 (3H, d, *J*, 6.5 Hz), 2.05 (1H, sept., *J* 6.5 Hz), 2.82 (2H, q, *J*, 6.5 Hz), 2.92 (2H, t, *J* 8.5 Hz), 3.19 (1H, q, *J* 6.5 Hz), 3.38 (1H, q, *J* 8.5 Hz), 3.54 (3H, m), 6.75 (1H, dd, *J*, 1.5, 7.5 Hz), 6.82 (1H, d, *J* 1.5 Hz), 6.99 (1H, d, *J* 7.5 Hz).
57		HCl. mp 161-163 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.91 (6H, dd, *J*, 1, 6.5 Hz), 1.31 (3H, d, *J* 6.5 Hz), 1.56 (2H, m), 1.65 (1H, sept, *J* 6.5 Hz), 2.92 (4H, m), 3.16 (1H, dt, *J* 5, 17.5 Hz), 3.47 (1H, q, *J* 9 Hz), 3.49 (1H, m), 3.53 (2H, m), 6.75 (1H, dd, *J*, 1.5, 7.5 Hz), 6.82 (1H, d, *J* 1.5 Hz), 6.99 (1H, *J* 7.5 Hz).
58		2HCl. mp 208-210 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.98 (2H, m), 1.20 (3H, m), 1.30 (3H, d, *J* 6.5 Hz), 1.71 (6H, m), 2.81 (2H, q, *J* 6.5 Hz), 2.91 (2H, t, *J* 8.5 Hz), 3.16 (1H, dd, *J* 6, 13 Hz), 3.39 (1H, q, *J* 8.5 Hz), 3.51 (3H, m), 6.75 (1H,

		dd, *J* 1.5, 7.5 Hz), 6.82 (1H, d, *J* 1.5 Hz), 6.99 (1H, d, *J* 7.5 Hz).
59		2HCl. mp 202-204 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.42 (3H, d, *J* 6.5 Hz), 2.92 (2H, m), 3.24 (1H, dd, *J* 6.5, 14 Hz), 3.38 (1H, q, *J* 9 Hz), 3.54 (2H, m), 3.68 (1H, q, *J* 7 Hz), 4.47 (1H, d, *J* 14 Hz), 4.58 (1H, d, *J* 14 Hz), 6.76 (1H, dd, *J*, 2, 8 Hz), 6.86 (1H, d, *J* 2 Hz), 6.99 (1H, d, *J* 8 Hz), 8.21 (2H, d, *J* 6.5 Hz), 8.94 (2H, d, *J* 6.5 Hz).

Example 60: (*S*)-1-(5-Fluoro-6-trifluoromethylindolin-1-yl)-2-propylamine fumarate



4-Fluoro-3-iodo-6-methylnitrobenzene

A solution of sodium nitrite (3.6 g) in water (20 mL) was added dropwise over 10 min to a stirred suspension of 2-fluoro-4-methyl-5-nitroaniline (8.5 g, 50 mmol) in concentrated hydrochloric acid (100 mL) at 0 °C. After a further 20 min at 0 °C the mixture was added over 5 min to a solution of potassium iodide (9.1 g, 55 mmol) in water (30 mL) keeping the internal temperature below 20 °C. After complete addition, the mixture was warmed to room temperature and stirred for 2 h then poured into water (500 mL) and extracted with ether (3 x 200 mL). The combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (500 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo* to leave the product as an orange oil. (400 MHz; $CDCl_3$) δ_H 8.41 (1H, d, *J* 6 Hz), 7.02 (1H, d, *J* 8 Hz), 2.59 (3H, s); GC (25 m Quartz/Bonded Phase I; Injection Temperature 250 °C; Detector Temperature 320 °C; Temperature Ramp Rate: 100 to 320 °C at 10 °C/min; Carrier Gas Helium; Flow Rate 12 mL/min) Retention Time: 5.92 min.

5-Fluoro-6-iodoindole

N,N-Dimethylformamide dimethylacetal (16.5 mL, 125 mmol) was added in one portion to a stirred solution of 4-fluoro-3-iodo-6-methylnitrobenzene (14.1 g, 50 mmol) in *N,N*-dimethylformamide (50 mL) at 130 °C under Ar. The mixture was stirred at 130 °C for 10 min then another aliquot of *N,N*-dimethylformamide dimethylacetal (10 mL) was added in one portion. The mixture was stirred at 130 °C for a further 10 min then another aliquot of *N,N*-dimethylformamide (6 mL) was added in one portion. The mixture was stirred at 130 °C for 10 min then poured into water (400 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL) then dried (magnesium sulfate), filtered and concentrated *in vacuo* to leave a solid. The solid was dissolved in acetic acid, ethanol (1:1; 240 mL) and iron powder (33.2 g, 600 mmol) was added in one portion. The mixture was placed under an atmosphere of Ar, heated to 90 °C and stirred for 15 min (CARE: VIGOROUS REACTION – COOLING MAY BE REQUIRED). After cooling to room temperature the mixture was filtered through celite and the filtrate was concentrated *in vacuo* to leave a crude oil. The oil was purified by column chromatography [SiO_2; dichloromethane, heptane (1:4 to 2:3)] to give the product (4.8 g, 37%, 3 steps from 2-fluoro-4-methyl-5-nitroaniline) as a green oil: NMR δ_H (400 MHz; $CDCl_3$) 8.18 (1H, br. s), 7.75 (1H, d, *J* 5 Hz), 7.32 (1H, d, *J* 8.5 Hz), 7.22-7.23 (1H, m), 6.50-6.52 (1H, m); GC (25 m Quartz/Bonded Phase I; Injection Temperature 250 °C; Detector Temperature 320 °C; Temperature Ramp Rate: 100 to 320 °C at 10 °C/min; Carrier Gas Helium; Flow Rate 12 mL/min) Retention Time: 8.65 min.

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-5-fluoro-6-iodoindole

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-5-fluoro-6-iodoindole was prepared according to General Method B, step (a) using 5-fluoro-6-iodoindole and (*S*)- 2-(tert-butoxycarbonylamino)propane methanesulfonate to give the product (1.0 g, 57%) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 3360, 2925, 2854, 1682, 1565, 1531, 1460, 1402, 1377, 1366, 1345, 1325, 1292, 1251, 1228, 1204, 1172, 1141, 1119, 1100, 1063, 1030, 974, 893, 859, 850, 812, 747, 721, 709, 655 and 596; δ_H (400 MHz; $CDCl_3$) 7.72 (1H, d,

J 4.5 Hz), 7.27 (1H, d, *J* 8.6 Hz), 7.06 (1H, d, *J* 3.5 Hz), 6.42 (1H, d, *J* 3.5 Hz), 4.36 (1H, br. s), 3.97-4.20 (3H, m), 1.41 (9H, s), 1.10 (3H, d, *J* 6.5 Hz).

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-5-fluoro-6-trifluoromethylindole

Methyl 2-chloro-2,2-difluoroacetate (3.0 ml, 28 mmol) was added in one portion to a stirred suspension of (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-5-fluoro-6-iodoindole (0.6 g, 1.4 mmol), copper(I)iodide (2.8 g, 14 mmol) and potassium fluoride (0.86 g, 14 mmol) in *N*,*N*-dimethylformamide (10 mL) under Ar. The mixture was heated to 120 °C and stirred for 2 h then poured into ethyl acetate (100 mL) and filtered through celite. The filtrate was concentrated *in vacuo* and purified by column chromatography [SiO_2; ethyl acetate-heptane (1:9)] to give the product (0.44 g, 84%) as a white solid: δ_H (400 MHz; $CDCl_3$) 7.62 (1H, m), 7.33 (1H, d, *J* 11 Hz), 7.23 (1H, d, *J* 3.0 Hz), 6.50 (1H, d, *J* 3.0 Hz), 4.37 (1H, br. s), 3.99-4.27 (3H, m), 1.37 (9H, s), 1.11 (3H, d, *J* 6.5 Hz); HPLC (Column: Supelcosil ABZ$^+$ [170 mm x 4.6 mm], particle size 5 μM; Eluent: methanol, 10 mM aqueous ammonium acetate solution (4:1); Flow Rate 1.0 mL/min; Detection Wavelength λ = 230 nM) Retention Time: 3.91 min.

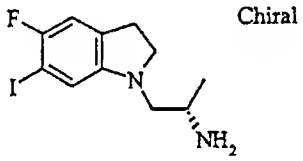
(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-5-fluoro-6-trifluoromethylindoline

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-5-fluoro-6-trifluoromethylindoline was prepared according to General Method B, step (b) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-5-fluoro-6-trifluoromethylindole as a white solid (0.25 g, 45 % yield): IR ν_{max} (Nujol)/cm^{-1} 6785, 3332, 2924, 2854, 1698, 1681, 1645, 1626, 1604, 1540, 1505, 1460, 1440, 1378, 1363, 1345, 1302, 1285, 1264, 1236, 1203, 1158, 1124, 1058, 1034, 1022, 984, 890, 870, 849, 799, 778, 751, 727 and 675; δ_H (400 MHz; $CDCl_3$) 6.85 (1H, d, *J* 9.6 Hz), 6.48 (1H, d, *J* 5 Hz), 4.45 (1H, br. s), 3.84-3.97 (1H, m), 3.48 (1H, dd, *J* 16.5 Hz, 8.7 Hz), 3.40 (1H, dd, *J* 16.5 Hz, 8.3 Hz), 2.95-3.04 (4H, m), 1.39 (9H, s), 1.19 (3H, d, *J* 6.9 Hz).

(*S*)-1-(5-Fluoro-6-trifluoromethylindolin-1-yl)-2-propylamine fumarate

(*S*)-1-(5-Fluoro-6-trifluoromethylindolin-1-yl)-2-propylamine fumarate was prepared according to General Method B, step (c) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-5-fluoro-6-trifluoromethylindoline as a white solid (0.08 g, 35%): mp 190-192 °C; IR ν_{max} (Nujol)/cm^{-1} 2923, 2854, 2535, 1710, 1627, 1501, 1454, 1398, 1378, 1346, 1285, 1234, 1162, 1121, 1041, 976, 877, 847, 798, 728, 652 and 590; δ_H (400 MHz, DMSO-d_6) 7.19 (1H, d, *J* 10.1 Hz), 6.81 (1H, d, *J* 5.4 Hz), 6.44 (2H, s), 3.59-3.63 (1H, m), 3.28-3.38 (3H, m), 2.91-3.06 (3H, m), 1.23 (3H, d, *J* 5.5 Hz).

Example 61: (*S*)-1-(5-Fluoro-6-iodoindolin-1-yl)-2-propylamine fumarate



(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl)-5-fluoro-6-iodoindoline

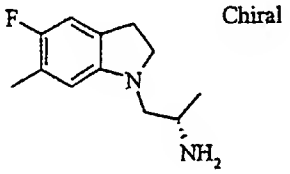
(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl)-5-fluoro-6-iodoindoline was prepared according to General Method B, step (b) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl)-5-fluoro-6-iodoindole as a white solid (1.6 g, 78%): IR ν_{max} (Nujol)/cm^{-1} 3343, 2925, 2854, 1698, 1679, 1646, 1604, 1583, 1535, 1498, 1469, 1405, 1390, 1378, 1363, 1291, 1265, 1253, 1228, 1172, 1129, 1113, 1053, 1034, 1016, 973, 954, 929, 892, 875, 850, 820, 776, 750, 726, 644, 598 and 593; NMR δ_H (400 MHz; $CDCl_3$) 6.77 (1H, d, *J* 7.2 Hz), 6.67 (1H, d, *J* 4.9 Hz), 4.48 (1H, br. s), 3.81-3.93 (1H, m), 3.39-3.48 (2H, m), 2.91-2.99 (4H, m), 1.43 (9H, s), 1.20 (3H, d, *J* 6.9 Hz).

(*S*)-1-(5-Fluoro-6-iodoindolin-1-yl)-2-propylamine fumarate

(*S*)-1-(5-Fluoro-6-iodoindolin-1-yl)-2-propylamine fumarate was prepared according to General Method B, step (c) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl)-5-fluoro-6-iodoindoline as a white solid (0.12 g, 55%): mp 185-187 °C; IR ν_{max} (Nujol)/cm^{-1} 3432, 3199, 2925, 2855, 2538, 1971, 1695, 1657, 1626, 1561, 1487, 1466, 1402, 1377,

1365, 1292, 1255, 1224, 1203, 1178, 1132, 1087, 1045, 1011, 980, 958, 944, 896, 859, 794, 735 and 647; NMR δ_H (400 MHz; DMSO-d_6) 6.99 (1H, d, J 8.2 Hz), 6.92 (1H, d, J 5.0 Hz), 6.46 (2H, s), 3.51-3.53 (1H, m), 3.21-3.31 (3H, m), 2.88-3.02 (3H, m), 1.22 (3H, d, J 6.5 Hz).

Example 62: (*S*)-1-(5-Fluoro-6-methylindolin-1-yl)-2-propylamine fumarate



(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-5-fluoro-6-methylindoline

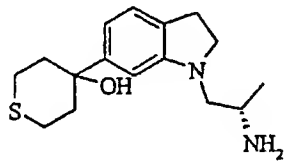
Triphenylphosphine (66 mg, 0.2 mmol) was added in one portion to a stirred solution of palladium(II) acetate (18 mg, 0.06 mmol) in tetrahydrofuran (2.5 mL) under Ar. The mixture was stirred for 5 min then a solution of (*S*)-1-[2-(tert-butoxycarbonylamino)propyl)-5-fluoro-6-iodoindoline (0.45 g, 1.1 mmol) in tetrahydrofuran (7.5 mL) was added in one portion. The mixture was stirred for 10 min then tetramethyltin (2.0 g, 11 mmol) was added in one portion. The mixture was heated to reflux and stirred for 168 h. After cooling to room temperature, the mixture was poured into an aqueous solution of potassium fluoride (50 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo* to leave a crude oil. The oil was purified by column chromatography [SiO_2; ethyl acetate-heptane (1:19)] to give the product (0.17 g, 50%) as a yellow solid; NMR δ_H (400 MHz; $CDCl_3$) 6.74 (1H, d, J 9 Hz), 6.22 (1H, d, J 5.9 Hz), 4.57 (1H, br. s), 3.82-3.91 (1H, m), 3.31-3.40 (2H, m), 2.89-2.99 (4H, m), 2.05 (3H, s), 1.44 (9H, s), 1.22 (3H, d, J 6.5 Hz).

(*S*)-1-(5-Fluoro-6-methylindolin-1-yl)-2-propylamine fumarate

(*S*)-1-(5-Fluoro-6-methylindolin-1-yl)-2-propylamine fumarate was prepared according to General Method B, step (c) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-5-

fluoro-6-methylindoline as a solid (0.08 g, 50%): LC Supelcosil ABZ$^+$ (170 mm x 4.6 mm: particle size 5μm), methanol/10 mM aqueous ammonium acetate, flow rate of 1.0 mL/min, λ_{det} = 254 nm, retention time = 2.64 min; NMR δ_H (400 MHz; DMSO) 6.86 (1H, d, *J* 9.5 Hz), 6.51 (2H, s), 6.45 (1H, d, *J* 6.7 Hz), 3.38-3.49 (1H, m), 3.19-3.27 (3H, m), 2.85-3.00 (3H, m), 2.15 (3H, s), 1.24 (3H, d, *J* 6.5 Hz).

Example 63: (*S*)-1-[6-(4-Hydroxytetrahydrothiopyran-4-yl)indolin-1-yl)-2-propylamine fumarate



(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-(4-hydroxytetrahydrothiopyran-4-yl)indoline

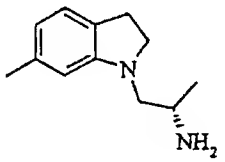
To a stirred suspension of potassium hydride (30% dispersion in mineral oil, 0.08 g, 0.60 mmol) in dry tetrahydrofuran (2 mL) at 0 °C, under argon, was added a solution of (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-bromoindoline (0.20 g, 0.60 mmol) in tetrahydrofuran (1 mL). After 15 mins, the solution was cooled to –78 °C and *tert*-butyl lithium (1.7 M, 0.68 mL, 1.2 mmol) was added dropwise. The mixture was stirred for a further 15 mins and then tetrahydrothiopyran-4-one (0.14 g, 1.2 mmol) was added portionwise. The solution was warmed gradually to room temperature, then diluted carefully with saturated ammonium chloride solution (10 mL). The mixture was extracted with ether (2 x 10 mL). The extracts were dried (magnesium sulfate), evaporated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (2:1)] to give the product (0.20 g, 90%). δ_H (400 MHz, $CDCl_3$) 0.88 (2H, t, *J* 7 Hz), 1.24 (3H, d, J 6.5 Hz), 1.42 (9H, s), 1.99 (1H, m), 2.03 (1H, m), 2.13-2.21 (2H, m), 2.44 (1H, m), 2.48 (1H, m), 2.99 (2H, t, *J* 9 Hz), 3.06 (1H, dd, *J* 5.5, 13.5 Hz), 3.22 (2H, dt, *J* 2.5, 9 Hz), 3.50 (2H, m), 3.94 (1H, m), 6.79 (2H, m), 7.07 (1H, *J* 7.5 Hz); HPLC (Column: Supelcosil ABZ$^+$ [170 mm x 4.6 mm], particle size 5 μM; Eluent: methanol,

10 mM aqueous ammonium acetate solution (4:1); Flow Rate 1.0 mL/min; Detection Wavelength λ = 230 nM) Retention Time: 3.51 min.

(*S*)-1-[6-(4-Hydroxytetrahydrothiopyran-4-yl)indolin-1-yl)-2-propylamine fumarate

(*S*)-1-[6-(4-Hydroxytetrahydrothiopyran-4-yl)indolin-1-yl)-2-propylamine fumarate was prepared according to General Method . B, step (c) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-(4-hydroxytetrahydrothiopyran-4-yl)indoline to give the product as a white solid (0.056 g, 51%). NMR δ_H (400 MHz, DMSO-d_6) 1.25 (3H, d, *J* 6.5 Hz), 1.81 (2H, m), 1.97 (2H, m), 2.36 (2H, m), 2.82 (1H, t *J* 6 Hz), 2.89 (2H, m), 2.99 (1H, dd, *J* 5.5, 14 Hz), 3.09 (2H, dt, *J* 2, 9 Hz), 3.27 (1H, m), 3.40 (1H, m), 3.47 (1H, m), 6.44 (2H, s), 6.72 (1H, brs), 6.74 (1H, dd, *J* 1.5, 7.5 Hz), 6.99 (1H, d, *J* 7.5 Hz); HPLC (Column: Supelcosil ABZ$^+$ [170 mm x 4.6 mm], particle size 5 μM; Eluent: methanol, 10 mM aqueous ammonium acetate solution (7:3); Flow Rate 1.0 mL/min; Detection Wavelength λ = 210 nM) Retention Time: 3.40 min.

Example 64: (*S*)-1-(6-Methylindolin-1-yl)-2-propylamine fumarate



(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-methylindoline

To a stirred suspension of palladium(II)acetate (0.012 g, 0.05 mmol) in THF (5 mL) under Ar was added triphenylphosphine (0.058 g, 0.22 mmol). The mixture was stirred for 10 min and (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-bromoindoline (0.39 g, 1.1 mmol) was added. The mixture was stirred for 10 min and methylboronic acid (0.13 g, 2.20 mmol) in ethanol (2 mL) followed by aqueous sodium bicarbonate solution (2M, 5 mL, 10 mmol) were added. The mixture was heated to reflux for 16 h, cooled to room temperature and partitioned between ether (25 mL) and water (2 x 25 mL). The organic layer was washed with brine, dried (magnesium sulfate), concentrated *in vacuo* and

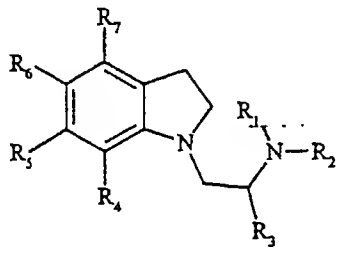
purified by column chromatography [SiO_2, heptane, ether (3:1)] to give the product as a white solid (0.07 g, 22%). δ_H (400 MHz, $CDCl_3$) 1.23 ((3H, d, *J* 6.5 Hz), 1.44 (9H, s), 2.28 (3H, s), 2.93 (2H, t, *J* 8.5 Hz), 3.04 (2H, m), 3.40 (2H, m), 6.30 (1H, s), 6.48 (1H, d, *J* 7.5 Hz), 6.96 (1H, d, *J* 7.5 Hz), (contains 25% des-methyl); HPLC (Column: Supelcosil ABZ$^+$ [170 mm x 4.6 mm], particle size 5 μM; Eluent: methanol, 10 mM aqueous ammonium acetate solution (4:1); Flow Rate 1.0 mL/min; Detection Wavelength λ = 230 nM) Retention Time: 4.18 min.

(*S*)-1-(6-Methylindolin-1-yl)-2-propylamine fumarate

(*S*)-1-(6-Methylindolin-1-yl)-2-propylamine fumarate was prepared according to General Method B, step (c) using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-methylindoline to give the product as a white solid (0.053 g, 79%). δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6.5 Hz), 2.21 (3H, s), 2.86 (2H, m), 2.97 (1H, m), 3.00 (1H, dd, *J* 5.5, 14 Hz), 3.24 (2H, m), 3.40 (1H, m), 6.45 (2H, s), 6.60 (1H, t, *J* 8 Hz), 6.94 (1H, d, *J* 7.5 Hz), 7.06 (1H, d, *J* 7.5 Hz) (contains 25% des-methyl); HPLC (Column: Supelcosil ABZ$^+$ [170 mm x 4.6 mm], particle size 5 μM; Eluent: methanol, 10 mM aqueous ammonium acetate solution (7:3); Flow Rate 1.0 mL/min; Detection Wavelength λ = 210 nM) Retention Time: 2.49 min.

CLAIMS

1. For use in therapy a chemical compound of formula (I):



(I)

wherein:

R_1 to R_3 are independently selected from hydrogen and alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen,

and pharmaceutically acceptable salts and prodrugs thereof.

2. A compound according to claim 1 wherein R_1 and R_2 are hydrogen.

3. A compound according to claim 1 wherein R_1 is hydrogen and R_2 is alkyl.

4. A compound according to claim 1 wherein R_1 is hydrogen and R_2 is arylalkyl.

5. A compound according to claim 1, 2, 3 or 4 wherein R_3 is alkyl.

6. A compound according to claim 1, 2, 3 or 4 wherein R_3 is methyl.

7. A compound according to any of claims 1 to 6 wherein R_4 is hydrogen or halogen.

8. A compound according to any of claims 1 to 7 wherein R_5 is selected from halogen, alkyl, aryl, alkoxy, alkylthio, monoalkylamino and dialkylamino.

9. A compound according to any preceding claim wherein R_5 is selected from alkylthio.

10. A compound according to any preceding claim wherein R_6 is selected from halogen and hydrogen.

11. A compound according to any preceding claim wherein R_7 is hydrogen.

12. A compound according to claim 1 wherein the compounds of formula (I) are selected from 1-(6-chloro-5-fluoroindolin-1-yl)-2-propylamine, 1-(5,6-difluoroindolin-1-yl)-2-propylamine, 1-(6-bromo-5-fluoroindolin-1-yl)-2-propylamine, 1-(6-bromoindolin-1-yl)-2-propylamine, 1-(6-chloroindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-trifluoromethylindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-methylthioindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-iodoindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-ethylthioindolin-1-yl)-2-propylamine, 1-(-5-fluoro-6-methylindolin-1-yl)-2-propylamine, 1-(6-methylthioindolin-1-yl)-2-propylamine, 1-(6-ethylthioindolin-1-yl)-2-propylamine, 1-(6-trifluoromethylindolin-1-yl)-2-propylamine, 1-(6-methoxyindolin-1-yl)-2-propylamine, 1-(6-propylthioindolin-1-yl)-2-propylamine, 1-(6-isopropylthioindolin-1-yl)-2-propylamine, 2-(6-chloroindolin-1-yl)-1-ethylamine, 2-(6-bromoindolin-1-yl)-1-ethylamine, 1-(5-chloroindolin-1-yl)-2-propylamine, 1-(5-fluoroindolin-1-yl)-2-propylamine and 1-(6-methylindolin-1-yl)-2-propylamine.

13. A compound according to any preceding claim wherein the compounds are selected from the (*S*)-enantiomers thereof.

14. A compound of formula (I) as set out in any one of claims 1 to 13, *per se*, wherein R_7 is selected from a group other than hydroxy.

15. A compound according to claim 14 wherein R_7 is hydrogen.

16. The use of a compound of formula (I) as set out in any of claims 1 to 13 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

17. A use according to claim 16 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

18. A use according to claim 16 wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

19. A use according to claim 18 wherein said toxic or infective CNS disease is encephalitis or meningitis.

20. A use according to claim 16 wherein the cardiovascular disorder is thrombosis.

21. A use according to claim 16 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility

22. A use according to claim 16 wherein said medicament is for the treatment of obesity.

23. A method of treatment of any of the disorders set out in claims 16 to 22 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 13.

24. A use or method according to any of claims 16 or 23 wherein said treatment is prophylactic treatment.

25. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 13.

26. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 13 in combination with a pharmaceutically acceptable carrier or excipient.

27. A method of making a composition according to claim 26 comprising combining a compound of formula (I) as set out in any one of claims 1 to 13 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Interr nel Application No
PCT/GB 99/02879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/08 A61K31/40 C07D401/04 C07D409/04 C07D409/12
C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32967 A (SMITHKLINE BEECHAM PLC) 7 December 1995 (1995-12-07) * page 8-9: description 3 and 4 *	13
X	EP 0 780 118 A (L' OREAL) 25 June 1997 (1997-06-25) page 18, line 10	13
A	EP 0 655 440 A (F. HOFFMANN-LA ROCHE AG) 31 May 1995 (1995-05-31) cited in the application * page 9, 12; claim 1 *	1,16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1999	08/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/02879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23-24
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 23-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Inter nal Application No
PCT/GB 99/02879

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